## TALKING SENSE *

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IF the technique of reducing ideas to a simple form, and placing them in logical order, were carried out extensively, only a few of our clinical ideas would come through unscathed.

"Our path is cumbered with guesses, presumptions and conjectures. The untimely and sterile fruitage of minds which cannot bear to wait for the facts, and are ready to forget that the use of hypotheses lies, not in the display of ingenuity, but in the labour of verification."—CLIFFORD ALLBUTT.

### Stress

Consider the ubiquitous stress factor, now accepted as the origin of many modern diseases—peptic ulcer, asthma, and ulcerative colitis. Here is a particularly well-written passage on this subject, from the pen of a distinguished physician:

"Peptic ulcer—one of the pestilent camp followers of civilization—one of the penalties we pay for our boasted progress, seems to be more than keeping pace with our advancement, and to be attaching itself especially to certain forms and phases of civilization. There is reason to believe that it is, if not of modern origin, at least of modern growth, and that modern habits and modern modes of life have something to do with its propagation. This is essentially a feverish and a fidgetty age, in which an unappeasable restlessness pervades all ranks and classes. The struggle for existence has become a melée, and the recommendation to 'commune with your own heart in your chamber, and be still' is looked upon as an obsolete adage. The result of all this ceaseless agitation and ambitious striving is that the gastric mucosa often gives way under the strain imposed on it. By a hideous kind of poetical justice, peptic ulcer has become a distorted reflection of the follies of the age. It is the miserable *otium cum dignitate* of the man of business."

May I now admit, with apologies, which are not very sincere, that I have been guilty of a trick. I deliberately altered two words in that passage. Wherever it said "G.P.I.", I substituted the words "peptic ulcer", and where it mentioned "the nervous system", I wrote in the words "gastric mucosa". Apart from that, those are the actual words spoken by Dr. James Crichton-Browne in 1871, about the cause of general paralysis of the insane, at the seventh meeting of the Medico-Psychological Association.[1] It makes one think. We hold such very different views about the cause of G.P.I. today. It can still provide *otium* for business men, but *cum* much less *dignitate*.

In the case of psychosomatic disease, are we not reasoning as follows: the pace of modern life is going up; the incidence of peptic ulcer is also going up; therefore the pace of modern life is the cause of peptic ulcer"? What price "guesses, presumptions, and conjectures"?

Why indeed is it so often presumed that the speed of civilisation always involves stress and strain? Crossing the Pacific in a Comet is less strain than crossing it in a coracle, and cave-men were probably as much troubled by shortages of suitable flints as modern man is troubled by his income-tax.

The danger of psychosomatic explanations for unexplained diseases is that they are so easy to find and provide such a comforting illusion that something has been explained, when it has not. That is why I regard Crichton-Browne's remarks on G.P.I. as a valuable warning.

### Comforting Illusions

It is important to recognise that things are much easier to believe if they are comforting, and that many clinical notions are accepted because they are comforting rather than because there is any evidence to support them. Just as we swallow food because we like it, and not because of its nutritional content, so do we swallow ideas because we like them and not because of their rational content.

Crawshay-Williams'[2] penetrating philosophical study of irrational thought called *The Comforts of Unreason* is a work I have found most enlightening, and its list of what he calls "comfortable concepts" is highly informative. One comfortable concept, which most of us accept without being aware of it, was heartlessly exposed by Dr. Ronald Bodley Scott in a previous Lettsomian lecture. "The science of therapeutics", he said, "is founded on the touchingly naïve assumption that there is an answer to every question it poses."[3] How uncomfortably true that is, and how few people have the courage to say it! We always say "What is the treatment of this disease?" rather than "Is there a treatment for this disease?" Even the expression "effective treatment" is a quaint one. We do not talk of "mobile motor-cars": we assume that they move, because that is their purpose and function. Logically we should not give treatment unless it is effective.

From this I obtain a concept which I believe to be true but which I find too depressing to accept: "It is better to believe in therapeutic nonsense than openly to admit therapeutic bankruptcy." (Better, in the sense that a little credulity makes us better doctors though worse research-workers.) I find this very uncomfortable. If you admit to yourself that the treatment you are giving is frankly inactive, you will inspire little confidence in your patients (unless you happen to be a remarkably gifted actor), and the results of your treatment will be negligible. But if you believe fervently in your treatment, even though controlled tests show that it is useless, then your results are much better, your patients are much better, and your income is much better too. I believe this accounts for the remarkable success of some of the less gifted but more credulous members of our profession, and also for the violent dislike of statistics and controlled tests which fashionable and successful doctors commonly display. It is an almost insoluble problem, and the majority of worth-while doctors are driven to a compromise in which they muster enough genuine belief in their treatment to keep their patients happy and maintain their own self-respect, while preserving enough doubt to admit their inadequacy during transient bouts of uncomfortable honesty.

* From the third Lettsomian lecture for 1959, delivered before the Medical Society of London on Feb. 16. An abbreviated version of the first lecture is appearing in the *British Medical Journal*. Extracts from the second lecture were published in *The Lancet* last week. The three lectures will later appear together in the *Transactions* of the society.

1. *J. ment. Sci.* 1871–72, **17**, 147.
2. Crawshay-Williams, R. London, 1947.
3. Scott, R. B. *Trans. med. Soc. Lond.* 1957, **73**, 132.

To avoid discovering the truth, because you do not think you will like it, seems too pusillanimous to contemplate. " Where ignorance is bliss, 'tis folly to be wise ", and I have sometimes wondered what is the point of controlled tests which only reveal therapeutic poverty.

For example, there is quite a large body of evidence that neither insulin nor electroconvulsion therapy affects the course of schizophrenia; but, if this evidence is accepted, we have to conclude that there is no treatment for schizophrenia except to keep the patient out of harm's way and to hope for the best. If this was openly admitted, the distress it would cause to thousands of patients and to their relatives is too sad to contemplate. Turning to less serious diseases, is there any pharmacological substance which affects the course of acne vulgaris or of chilblains? —one that would give significantly better results than its inert counterpart in a double-blind trial? The many remedies we prescribe for these conditions—are they better than nothing, or exactly the same as nothing? If we accept that often the effect of our treatment is unrelated to its pharmacological content, would it be more sensible to prescribe an inert and harmless substance which is also cheap? We are certainly not encouraged to do so: in the whole of our *National Formulary* there is no intentionally inert preparation. No tab. dulcis fanny-adamis co. No mist. oculi mei cum betty-martini. And what an outcry there would be if there were!

So let us face the fact that, until we have effective remedies for every complaint, we must cherish our delusions of therapeutic omnipotence, even though Bodley Scott may call us touchingly naïve. But let us at least have brief moments of uncomfortable discernment, so that we can separate those remedies which depend on faith from those which depend on pharmacy. We must keep enough faith in our treatment to make ourselves and our patients happy, and yet enough doubt to make us aware of the need for something better.

The laity are equally prone to adopt comfortable concepts. One of the most irrational and comforting delusions held by the layman is the notion that his body is really a kind of motor-car. " I feel much better now you've given me a thorough overhaul " is a remark I have heard on many occasions. Doctors are often guilty of nourishing this delusion when they make remarks such as " You'd better come in for a complete check-up ". Behind all this lies the delusion that the physician is likely to remedy defects as he finds them—applying a little oil here, fitting a replacement there, and possibly clearing out a blocked pipe. Business men and high-up executives like to have " complete check-ups " at regular intervals, when they can go into a clinic for a lot of expensive investigations. This emphasises their importance (" we always have the Rolls decarbonised every 5000 miles to keep it in tip-top condition, but we don't bother about the utility van "), and also it gives them a feeling of security, as they come out of the clinic rejuvenated by a comforting illusion of physical decarbonisation. But the analogy with motor-car engines is false, and the only point where it applies is that when the trouble is very serious the patient is likely to be returned to his Maker.

### Uses of Logic

Some teachers say that medical thinking would be more rational if doctors were taught logic. I rather doubt this. Most of our ideas are accepted because they are convenient or likely, and not because of logical reasoning. Even with research a good deal of the reasoning is put in after the discovery has been made. Sir Charles Dodds once compared research to the progress of a man stumbling across a dark room, trying to find the light switch and upsetting the furniture as he goes. Once he has found the switch and the light is on, he goes back and puts all the furniture tidy again.

Formal logic is based largely on statements of the kind:

All $x$ is $y$. All $y$ is $z$. Therefore all $x$ is $z$.

For instance:

All men are mortal. Socrates is a man. Therefore Socrates is mortal.

Medical facts are rarely suitable for this discipline. They are more of this kind:

Some $x$ is $y$, but I'm not really sure of it. Possibly all $y$ may be $z$ (as Smith has claimed to show), but Brown affirms that no $y$ is ever the slightest $z$, and Robinson too has strong views (though I find them hard to understand because he uses $x$ to mean either $y$ or $z$, and what I call $z$ he labels $y$.

All the same, a knowledge of elementary logic might make us more critical of the reasons we have for holding the opinions that we do. For example, consider the condition called iron-deficiency anæmia.

It is well known what type of anæmia follows inadequate intake of iron. We recognise it from the small pale cells which show more variation in size than is normal; we treat it confidently with oral or parenteral iron; and the hæmoglobin usually rises. But unconsciously we are arguing thus:

Iron lack is known to produce a hypochromic microcytic anæmia. This woman has a hypochromic microcytic anæmia. Therefore she has iron deficiency.

It would be almost equally rational to say:

This woman is weak. Addison's disease produces weakness. Therefore we must treat her for Addison's disease.

I do not deny that most cases of hypochromic microcytic anæmia are caused by lack of iron, but I do criticise the term " iron-deficiency anæmia " to describe the appearance of the film. First, because this is unjustifiable in logic; secondly because it involves naming by supposed cause and not by observed fact; and thirdly because it contains an important assumption. It assumes that this anæmia is an illness—that something is wrong, and that it needs putting right. This assumption may be correct, but we ought to be aware of it.

We could make two quite different statements, the first with this assumption and the second without it:

*A*. Iron-deficiency anæmia is very common in pregnant women, more than half of whom show hæmoglobin levels under 70%, which respond well to iron therapy.

*B*. During pregnancy, the normal hæmoglobin level falls below 70% in more than half the cases. This physiological change is prevented from taking place if there is an excess of iron in the diet.

I am not suggesting that either of these statements is true. I am only anxious to demonstrate how an observation can be interpreted in entirely different ways, according to whether you assume the condition is an illness or not, and to show how easy it is to make such an assumption without knowing it. You cannot say what things are abnormal till you have agreed on what is normal. You cannot describe *dis*ease without describing *ease* first.

This cardinal principle is often forgotten—as it applies to the word " constipation ", for instance.

Here we have all the elements of confusion. First are we naming the state of the bowels or the symptoms we attribute to that state? Secondly, are we naming an abnormality, or making a neutral statement about a function? If a man's bowels are usually open on alternate

days, and he comes into hospital 36 hours after they were last open do we correctly write in the notes " constipated for 36 hours ", or does this not differ in meaning from the statement " bowels last open 36 hours ago "? It is too easy to assume that the frequency or regularity of normal bowel action has been decreed by some natural law. We behave as if the human colon had been supplied with a maker's tag reading " This tube should be cleared out once every 24 hours ". We never lay down a statutory number of times that the bladder should be emptied each day. Why not? Why do we do so with the bowels? What is constipation? I looked the word up in my dictionary and it said " costiveness ". Then I looked up the word " costive " and it said " constipated ". So I cannot answer the question, or the many others I raised in connection with it.

I can only reiterate Allbutt's words: " Our path is cumbered with guesses, presumptions and conjectures."

* * *

I turn with relief to the more solid ground of common sense—the capacity to see the obvious even amid confusion, and to do the obviously right thing instead of working to rule.

When I was a boy, I was skating on the lake of Earls Colne Priory, when a lady fell and broke her leg. Many of the bystanders were acquainted with the rules of first aid and knew just what to do—" Keep her warm " and " Do not move her till the doctor comes." Maids hurried from the house with hot drinks, hot-water bottles, and luxurious furs: nutria lay upon beaver, and musquash was piled on mink. I skated gently round the stricken lady who groaned beneath her expensive load. The doctor seemed to be hours coming; so more hot bottles were added. Suddenly a matter of elementary physics began to be apparent: *warmth melts ice.* There were ominous cracking sounds; first-aid principles were forgotten, common sense was remembered—and we got her off the ice just in time. A few more seconds and that lady, together with a very valuable collection of furs, would have been lost.

# BENIGN STREPTOCOCCAL SORE THROAT

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STREPTOCOCCAL sore throat is important both as a common cause of sickness and because it may be followed by rheumatic fever or acute nephritis. Only cases of sore throat in which hæmolytic streptococci are implicated run the risk of rheumatic fever or nephritis, but these cannot be distinguished clinically from non-streptococcal cases (Landsman et al. 1951, Bishop et al. 1952). Because of this, Rammelkamp (1952) and the Committee on Prevention of Rheumatic Fever (1955) have pressed for treatment of all cases of acute sore throat with antibacterial substances, on the grounds that this will curtail the acute illness (Wannamaker et al. 1951, Houser et al. 1953), and reduce the risk of rheumatic fever (Catanzaro et al. 1958). These grounds, however, are insecure for a number of reasons.

The evidence that the clinical course of the sore throat is materially altered by antibiotic treatment is far from convincing (Brumfitt and Slater 1957).

The actual risk of rheumatic fever is difficult to assess. In Miami, Saslaw and Streitfeld (1956) were unable to find any cases of rheumatic fever in 7070 schoolchildren with persistent group-A streptococci in the throat, and a significant rise of antistreptolysin-O (A.S.O.) titre. Bywaters reports that first attacks follow streptococcal sore throat in about 0·1% of schoolchildren, and, in a Dr. Barnardo's Home, Holmes and Williams (1958) found no case of rheumatic fever in a thirty-month period during which nearly 300 cases of streptococcal sore throat occurred.

By contrast, in young American airmen Rammelkamp et al. (1951) found, in different series, that rheumatic fever followed untreated sore throat in 1·5 to 4·5% of their patients. In epidemics of streptococcal infection, Paul (1957), reviewing the literature, reports a rheumatic-fever attack-rate of up to 21%. The incidence of rheumatic fever in this country, even in groups of young adults comparable with Rammelkamp's, is unknown.

These difficulties would matter little if antibiotic therapy were free from risk. Since this is not so (Brown 1948, 1956, Feinberg and Feinberg 1956, Guthe et al. 1958, Herrell 1958), we need to know the relative risk of giving or withholding antibiotics.

Many factors have been held responsible for the reported variable incidence of rheumatic fever, but differences in the type of streptococcal sore throat have not been thought important. From an analysis of (*a*) the spread of streptococci in a closed community and (*b*) cases of sore throat derived from similar communities, we have concluded that the role of the hæmolytic streptococcus in sore throat must be reconsidered. In particular, we wish to define a form of sore throat from which hæmolytic streptococci can be isolated which appears to carry a very low risk of rheumatic fever. This we have called benign streptococcal sore throat.

## Materials and Methods

*Carrier-rate*

The carrier-rate of throat organisms was determined each month by swabbing the throats of recruits within one hour of their first arriving at the R.A.M.C. depot, Crookham, Hants. After living at the depot for three to four weeks, the same men were re-examined. They had not been out of the barracks during the interval. Cases of sore throat arising in this period were notified. At other depots, the carrier-rate was also determined among soldiers sleeping in the same barrack rooms as cases of known streptococcal sore throat.

*Clinical Cases*

The study of acute sore throat covers three periods: February to April, 1954; January to December, 1955; and July to August, 1956. During this time 242 patients were admitted to a special ward at the Cambridge Military Hospital, Aldershot. All these patients fulfilled the following clinical criteria: (1) the primary complaint was sore throat; (2) pyrexia was present (100·3°F on any one occasion, or 99·3°F on two or more occasions within twenty-four hours); (3) admission was within seventy-two hours of the onset of sore throat; (4) there was no clinical evidence of more generalised disease of which sore throat may have been a feature (e.g., glandular fever).

The patients, aged 17–22, came from the depots of other regiments in the Aldershot area, where they lived in conditions essentially similar to those at the R.A.M.C. depot. Of the 242 patients, 135 were treated with aspirin gargle alone (76 comprised a consecutive series, and 59 were part of a controlled trial to assess the effect of penicillin therapy). The remaining 107 patients were all treated with penicillin (62 as part of the controlled trial). The detailed management of these patients has already been described (Brumfitt and Slater 1957).

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Four to five weeks after the onset of sore throat, the patients were re-examined and questioned with particular reference to symptoms suggesting rheumatic fever or acute nephritis. The urine was examined for protein, and 12-lead electrocardiography was performed on all patients with a pulse-rate over 90 per minute. Information about the 9% of patients who defaulted was obtained by telephone or letter in every case. The diagnostic criteria of rheumatic fever (Slater and Rosenbaum 1959) were based upon those of Jones (1944) and were almost the same as the criteria used in the Anglo-American Therapeutic Trial (1955).

*Laboratory Methods*

*Culture of organisms.*—Throat swabs were taken using a dry sterile pledget of cotton-wool on a wooden applicator, and inoculated on two 5% horse-blood agar plates within one hour of being taken. One plate was incubated aerobically and the other anaerobically. After overnight incubation, colonies surrounded by beta hæmolysis were stained by Gram's method to distinguish hæmolytic streptococci from *Hæmophilus hæmolyticus* (which could not be confidently distinguished on colonial appearances alone). Hæmolytic streptococci were separated in pure culture, and their Lancefield group determined by the methods of Maxted (1948, 1954). The Griffith type of 52 group-A streptococci were determined by Dr. R. M. Fry of the Public Health Laboratories, Cambridge. Throat swabs were repeated daily while the patients were in hospital, and again three to four weeks after discharge.

*White-cell count.*—Total and differential counts were made on admission and, where abnormal values were found, repeated every few days. Particular care was taken to exclude glandular fever using the methods described by Brumfitt and O'Grady (1958).

*Serological examinations.*—Specimens of blood were obtained on admission and three to four weeks later. A.S.O. titres were estimated in 155 cases by Dr. R. M. Fry. All sera were examined by the screening test for glandular fever (Brumfitt and O'Grady 1957). Where this was positive, the Paul-Bunnell absorption test (Davidsohn 1937) was carried out. A search for antibody against influenza A, B, and C, psittacosis, Q fever, and streptococcus MG was made in most cases.

*Adenovirus studies.*—Examination for adenovirus was made in two separate periods during the investigation. On the first occasion 22 cases were examined, and on the second 20 cases. A second swab was taken on admission and inoculated into buffered saline, containing penicillin and streptomycin, and stored at −20°C. Virus isolation was attempted later by growth in HeLa cells in roller tubes by Dr. C. M. Becker at the Wright-Fleming Institute of Microbiology, St. Mary's Hospital. Serum obtained on admission and three to four weeks later was examined for adenovirus complement-fixing antibodies.

## Results

*Carrier-rates at the R.A.M.C. Depot*

Of 637 recruits examined on arrival at the depot, 15% (12·5–20%) were carrying hæmolytic streptococci, 8% (5–11%) being of group A, and 7% (5–13·5%) not of group A. *Streptococcus pneumoniæ* was carried by 24% (17–33%) (table I).

TABLE II—CLINICAL FEATURES IN ACUTE SORE THROAT ON ADMISSION

| — | Group-A streptococci isolated (160 patients) | Group-A streptococci *not* isolated (82 patients) |
|---|---|---|
| *Symptoms:* | | |
| Dysphagia | 83 (52%) | 53 (65%) |
| Headache | 87 (54%) | 44 (54%) |
| Abdominal pain and/or vomiting | 31 (19%) | 2 (2%) |
| Nasal discharge | 39 (24%) | 15 (18%) |
| Hoarse voice | 8 (5%) | 8 (10%) |
| Productive cough | 16 (10%) | 21 (25%) |
| *Signs:* | | |
| Faucial exudate | 128 (80%) | 57 (69%) |
| Temperature over 101°F | 111 (69%) | 57 (69%) |
| Enlarged lymph-nodes: | | |
| Anterior cervical | 111 (69%) | 40 (49%) |
| Posterior cervical | 83 (52%) | 44 (54%) |
| Marked pharyngeal injection | 125 (78%) | 37 (45%) |
| Leucocytosis (over 12,000 per c.mm.) | 112 (70%) | 49 (60%) |
| *Complications:* | | |
| Quinsy | 1 | 8 (10%) |
| Ulcers of mouth | 0 | 5 (6%) |
| Bronchopneumonia | 0 | 2 (2%) |
| Rheumatic fever (relapse) | 1 | 0 |

After about four weeks of barrack life a uniform rise in the carrier-rates had occurred in all the organisms studied except *H. hæmolyticus* which showed a very sharp midsummer peak. This rapid spread of organisms, which in the case of *H. hæmolyticus* in July and August involved 35% of the population, was not associated with any case of sore throat which satisfied our criteria.

*Clinical Features of "Streptococcal Sore Throat"*

Table II shows that no consistent clinical differences separated patients harbouring group-A streptococci from those who did not. But a rapid onset with abdominal pain and vomiting was often seen in the streptococcal cases, whereas evidence of a more diffuse respiratory illness, such as hoarseness and productive cough, was more common in the nonstreptococcal group.

*Complications*

No patient developed a first attack of rheumatic fever, but one man aged 18, who had had a previous attack, developed rheumatic carditis. He had been treated with aspirin gargles. Another patient, aged 19, who had received a four-day course of intramuscular penicillin developed acute nephritis after a sore throat from which Griffith type-12 streptococci had been isolated.

No suppurative lesions occurred after admission to hospital among those treated with aspirin gargles. 1 patient whose throat swab grew commensal organisms only developed aspiration pneumonia despite penicillin therapy. At the time of follow-up, no cases of poststreptococcal malaise, of the type described by Rantz et al. (1947), and no electrocardiographic abnormalities, were found.

*Recovery of Hæmolytic Streptococci*

Analysis of the cases of sore throat admitted to the ward in 1954, 1955, and 1956 revealed recovery-rates of hæmolytic streptococci much in excess of those observed

TABLE I—ORGANISMS ISOLATED FROM THROATS OF RECRUITS ON ARRIVAL AND AFTER 3–4 WEEKS AT R.A.M.C. DEPOT

| Month of examination | Group 1 May–June | | Group 2 June | | Group 3 July–Aug. | | Group 4 August | | Group 5 November | | Group 6 Nov.–Dec. | | Group 7 Nov.–Dec. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A* | B† | A | B | A | B | A | B | A | B | A | B | A | B |
| Number examined | 76 | 60 | 35 | 28 | 188 | 102 | 40 | 33 | 166 | 84 | 92 | 70 | 40 | 44 |
| Total hæmolytic streptococci (including group A) (%) | 18·5 | 20·0 | 14·5 | 7·0 | 12·5 | 17·5 | 15·0 | 21·0 | 14·5 | 19·0 | 19·5 | 27·0 | 20·0 | 27·0 |
| Hæmolytic streptococci group A (%) | 5·0 | 6·5 | 8·5 | 7·0 | 7·5 | 11·0 | 7·5 | 15·0 | 8·5 | 12·0 | 11·0 | 17·0 | 7·5 | 20·5 |
| *Str. pneumoniæ* (%) | 26·0 | 27·0 | 17·0 | 21·0 | 22·0 | 27·5 | 25·0 | 33·5 | 20·0 | 19·0 | 33·0 | 38·5 | 27·5 | 30·0 |
| *H. hæmolyticus* (%) | 10·5 | 6·5 | 0 | 3·5 | 10·5 | 35·0 | 0 | 3·0 | 0 | 5·0 | 0 | 0 | 0 | 0 |

* A, on arrival. † B, after three to four weeks at depot.

at the R.A.M.C. depot in 1955 (table III). This excess was composed of group-A hæmolytic streptococci. The recovery of both non-group-A hæmolytic streptococci and *Str. pneumoniæ* was of the same order as the November–December rates prevailing in the R.A.M.C. depot community after two to three weeks of barrack life (non-group-A streptococci: depot 10%, cases 9%. *Str. pneumoniæ*: depot 38%, cases 39%). The rate of recovery of group-A streptococci was, however, distinctly higher (depot 17%, cases 57–88%) (see table I, group 6, and table III). It is significant that the peak (88%) occurred when the cases were fewer, emphasising that they did not constitute part of an epidemic.

*Griffith Typing of Streptococci*

There was no evidence that any type spread more readily or was specifically associated with sore throats.

Types 3, 6, 19, 24, and 28 were recovered both from depot carriers and from the cases. Types 3 and 19 (found in 21% and 26% respectively) were the commonest. Types 8, 12, and 14 were each recovered from single cases. Of the depot recruits who carried streptococci at both examinations, 55% had the same type; and type 28 always persisted.

*Antistreptolysin-O Titres*

The findings are summarised in table IV. Among the 62 patients from whom no group-A streptococci were isolated, no significant changes occurred in the A.S.O.

TABLE III—RECOVERY OF HÆMOLYTIC STREPTOCOCCI FROM CASES IN 1954 AND 1956 AND CASES AND CONTACTS IN 1955

| — | Number of cases | Group-A hæmolytic streptococci | Non-group-A hæmolytic streptococci | Normal flora |
|---|---|---|---|---|
| 1954 | | | | |
| Feb.–April .. | 65 | 42 (*65%*) | 13 (*20%*) | 10 (*15%*) |
| 1955 | | | | |
| Jan.–March .. | 53 | 35 (*66%*) | 4 (*8%*) | 14 (*26%*) |
| April–June .. | 25 | 22 (*88%*) | 0 | 3 (*12%*) |
| July–Sept. .. | 21 | 13 (*62%*) | 4 (*19%*) | 4 (*19%*) |
| Oct.–Dec. .. | 43 | 28 (*65%*) | 4 (*9%*) | 11 (*26%*) |
| 1956 | | | | |
| July–Aug. .. | 35 | 20 (*57%*) | 3 (*9%*) | 12 (*34%*) |
| 1955 | Contacts | | | |
| July–Sept. .. | 56 | 38 (*68%*) | 5 (*9%*) | 13 (*23%*) |

titres of those treated with penicillin. Of those treated with aspirin alone, 1 showed a two-tube rise. In the group of 63 patients from whom group-A streptococci were isolated, and who received nonspecific treatment, 10 (16%) showed a two-tube rise whilst among the 30 receiving penicillin only 1 (3%) showed a two-tube rise.

*White-cell Count*

A leucocytosis of 12,000 cells per c.mm. or more was not always found in the patients harbouring streptococci. In fact, the frequency of this finding was not strikingly different in the two groups. No case showed the white-cell abnormalities characteristic of glandular fever (Brumfitt and O'Grady 1958) and Paul-Bunnell tests were all negative.

*Adenovirus Studies*

Adenovirus isolation was successful in 5 of the first group of 22 cases in which it was attempted.

Acute and convalescent sera were obtained from 3 of these patients and all showed a significant rise in titre. Paired sera were obtained from 7 patients in whom virus isolation failed, and a significant rise in titre was found in 3 of them. Streptococci were isolated in 15 of the 22 cases. 6 belonged to group A. 1 patient from whom adenovirus was isolated also harboured group-A streptococci in the throat. In the second group of 20 patients there were no successful virus isolations.

TABLE IV—ANTISTREPTOLYSIN-O TITRES AMONG PATIENTS FROM WHOM GROUP-A STREPTOCOCCI WERE, AND WERE NOT, ISOLATED

| — | No. of cases | | | |
|---|---|---|---|---|
| | Group-A streptococci isolated | | Group-A streptococci not isolated | |
| | Non-specific treatment | Penicillin treatment | Non-specific treatment | Penicillin treatment |
| Two-tube increase .. | 10 (*16%*) | 1 | 1 | 0 |
| One-tube increase .. | 14 | 13 | 10 | 2 |
| No increase or decrease.. | 39 | 16 | 38 | 11 |
| Total number of patients | 63 | 30 | 49 | 13 |

No evidence of infection with other respiratory viruses was obtained.

## Discussion

On arrival at the R.A.M.C. depot, about 8% of healthy recruits carried group-A streptococci in their throats. There was no widespread dissemination of streptococci after two to three weeks of communal living, but a slight increase in the carrier-rate was found. This spread of group-A streptococci was not associated with sore throats, as defined by Brumfitt and Slater (1957).

In contrast, group-A streptococci were isolated from 57–88% of the patients with acute sore throat admitted to hospital. These patients came from the large military depots in and around Aldershot, and did not appear to constitute part of an outbreak or outbreaks of acute sore throat. The failure to isolate streptococci from *all* the cases of sore throat is unlikely to be due to technical errors since daily throat swabs were examined, the swabs were plated with little delay, and the methods used are satisfactory (Brumfitt and Masters 1959).

In spite of this apparently different ætiology, streptococcal and non-streptococcal cases could not be distinguished clinically with confidence. This is in keeping with the experience of other workers (Commission on Acute Respiratory Diseases 1944, Landsman et al. 1951, Bishop et al. 1952), although Breese and Disney (1954) were more successful. In addition, the isolation-rate of hæmolytic streptococci from healthy contacts of cases from whom this organism was isolated was almost as high as that from the cases themselves.

The question therefore arises whether the position of the hæmolytic streptococcus as the primary cause of "streptococcal sore throat" can be maintained. It is possible that all these cases which share the same clinical features have a common primary ætiology, but that some become superinfected with hæmolytic streptococci. The ability of certain virus diseases to facilitate nidation and dissemination of hæmolytic streptococci is well established (Coburn and Pauli 1941, Hamburger 1944).

Nevertheless, in favour of an important role for the hæmolytic streptococcus is the finding that bacteriologically the depot community and the patients with sore throats differed only in the much higher isolation-rate of group-A streptococci from the patients. In addition, the rise in A.S.O. titre found in 16% of the 63 patients harbouring streptococci would be regarded by the Commission on Acute Respiratory Diseases (1944) as evidence of primary streptococcal infection. The limited effect of penicillin on the course of the illness, coincident with the elimination of streptococci from the throat, also suggests that this organism is implicated.

None of these observations, however, establish the streptococcus as the *primary* ætiological agent. It is to be expected that invasion of the throat by this organism, even if facilitated in some way, would be followed in a

proportion of cases by an antibody response. Equally, penicillin should control any aspect of the illness produced by the streptococcus. It seems quite possible, in fact, that there is a variety of acute sore throat in which the hæmolytic streptococcus plays an opportunist role. In this variety, streptococcal invasion occurs in only a few cases and rheumatic fever seldom follows.

Our patients seem to have suffered from this benign type, which we believe differs in its major characteristics from primary streptococcal sore throat. The cases were sporadic; only two-thirds of all patients with sore throat harboured streptococci, and the streptococcal and non-streptococcal cases were indistinguishable clinically; only 16% of those with streptococci showed a rise in A.S.O. titre; the carrier-rate in healthy contacts was high; and no first attacks of rheumatic fever occurred.

In contrast with this type of disease, it is possible, as early workers postulated (Griffith 1934), that, as a result of repeated passage or other factors, exalted streptococcal virulence might develop and cases of primary streptococcal sore throat appear. The characteristics of this kind of disease are seen in epidemics of streptococcal sore throat such as that described by the Commission on Acute Respiratory Diseases (1944).

This was a foodborne epidemic which affected 260 men in six weeks. The primary attack-rate was 42%. Type-5 group-A streptococci were recovered from all the patients and 80% showed a significant rise in A.S.O. titre. The case/carrier ratio was 10/1. 3 definite and 2 suspected cases of rheumatic fever occurred among 100 patients who were specially studied.

This disease stands in striking contrast to benign streptococcal sore throat. It occurs in epidemic form; the streptococcal isolation-rate is 100%, and a significant rise of A.S.O. titre occurs in a high proportion of cases. As almost all those who acquire such an organism develop clinical disease, the contact carrier-rate is low. We suggest that it is this disease which carries a high risk of rheumatic fever.

Rammelkamp et al. (1952) comment on the importance of crowding in increasing the incidence of rheumatic fever, and quote rates of up to 3·9% in *epidemics* of streptococcal disease. Lazar et al. (1957) describe a period of rapid increase in intake of United States Air Force recruits, during which half of one group living in the camp for about eight weeks developed sore throat. A total of 58 cases of rheumatic fever were encountered, including 5 which occurred within one period of twenty-four hours.

In sampling large and scattered populations, the variable presence of small outbreaks of primary streptococcal sore throat, together with the benign form, would explain most of the differences in the reported incidence of complications.

The difficulty of recognising localised outbreaks of streptococcal sore throat in conditions where streptococci could be recovered from the throats of many of the population was long ago emphasised by Coburn and Pauli (1941). The results of Rammelkamp et al. (1952) differ from the present series in a way which suggests that they were dealing with cases of which a proportion were of the primary streptococcal type. A significant rise of A.S.O. titre occurred in 60–70% of the untreated cases. Rheumatic fever was most common (4·1%) when the isolation-rate of streptococci from the throat was highest, falling to 1·5% when streptococci were less frequently recovered.

If the risk of complications is to be assessed adequately, it becomes important to distinguish between two types of diseases which are bacteriologically and probably clinically identical. If we add to this problem the variable incidence of carditis in rheumatic fever at different ages, the occurrence of rheumatic fever without preceding sore throat, and the frequent development of rheumatic heart-disease without overt rheumatic fever, the difficulty of assessing the long-term risk of withholding specific antibiotic therapy for acute sore throat becomes apparent. In retrospect, some help in differentiation can be gained from a study of carrier-rates and A.S.O. responses, but obviously neither can contribute to the assessment of risk in the individual patient.

As a guide to general policy it appears from the reported series (Chapple et al. 1956, Landsman et al. 1951, Holmes and Williams 1958) that in this country most cases of *sporadic* sore throat from which hæmolytic streptococci are isolated are of the benign form. In young adults the risk of rheumatic fever is probably very small, and specific treatment of benign streptococcal sore throat makes little difference to the five-day natural course of the acute illness. Although adequate penicillin treatment will prevent subsequent rheumatic fever (Denny et al. 1950), penicillin reactions may be dangerous, or even fatal (Feinberg and Feinberg 1956, Guthe et al. 1958), and are likely to become more common.

In contrast, patients who have had rheumatic fever in the past (in whom the dangers of streptococcal infection are much greater) must be treated with adequate amounts of penicillin. Similarly, during epidemics of streptococcal infections, when organisms of exalted virulence may appear, both prophylaxis and adequate therapy are indicated, even in those without previous rheumatic disease. Adequate treatment means a course of penicillin long enough to eradicate the streptococcus from the throat (Catanzaro et al. 1954). A four-day course of short-acting intramuscular penicillin is too short (Brumfitt and Slater 1957), and a form of penicillin treatment that is effective for seven to ten days should be used instead (McEwen 1954).

If in benign streptococcal sore throat the streptococcus is always a secondary invader, the identification of the primary agent would be most valuable. The present work suggests that it is neither adenovirus nor the agent of glandular fever, although they may co-exist with streptococci in the throat.

**Summary**

The significance of Lancefield group-A streptococci in acute sore throat has been assessed by studying the spread of this organism in a closed healthy community, and the isolation-rates from patients from similar populations with sporadic acute sore throat.

Lancefield group-A streptococci were isolated from 5–11% of the close community and this increased to 6·5–20·5% after three to four weeks of communal life without cases of sore throat occurring. In contrast, group-A streptococci were isolated from 57–88% of the patients with sore throat.

Streptococcal and non-streptococcal cases were indistinguishable clinically. Only 16% of patients with group-A streptococci showed a significant rise in anti-streptolysin-O titre. No first attacks of rheumatic fever were seen.

The isolation of group-A streptococci in patients with acute sore throat does not necessarily imply that streptococci are the primary cause of the illness. Most of our patients seem to have suffered from a benign form of streptococcal sore throat in which the streptococcus played an opportunist role.

It follows that treatment with penicillin should be

reserved for patients who have had rheumatic fever in the past, and for epidemics of streptococcal infection, when organisms of enhanced virulence may appear. If given, the course of penicillin should be adequate, and should last about seven to ten days.


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## EVIDENCE FOR THE EXISTENCE OF THE HUMAN "SUPER FEMALE"


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THREE groups of human beings with abnormal chromosome numbers have now been described. One of these, the mongols, has been shown to have 47 chromosomes, the additional chromosome being a small acrocentric autosome (Lejeune, Gauthier, and Turpin 1959, Jacobs, Baikie, Court Brown, and Strong 1959). In the other two groups there are abnormalities of the number of the sex chromosomes. In the chromatin-positive form of Klinefelter's syndrome, a chromosome number of 47 has been found and a chromosomal sex of XXY (Jacobs and Strong 1959); while in the second group, consisting of apparent females with Turner's syndrome who are chromatin-negative on nuclear sex determination, the chromosomal number is 45 and the chromosomal sex is XO (Ford, Jones, Polani, Almeida, and Briggs 1959).

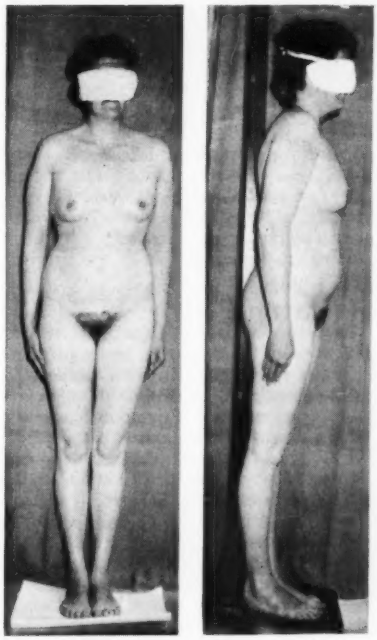

Fig. 1—Present appearance of patient.

This present report concerns a third type of sex-chromosome anomaly—namely, the "super-female", characterised by a chromosomal number of 47 and a chromosomal sex of XXX.

### Case and Investigation

*Clinical Data*

The patient, born in 1924, is the youngest of a sibship of three girls. At the time of the patient's conception her mother was 41 years of age and her father was probably 40. As far as is known she is the product of a full-term normal pregnancy.

She was first seen by one of us (T. N. M.) in 1946 because of secondary amenorrhœa. Menstruation is thought to have begun in 1938, at the age of 14, and from the onset it was irregular, occurring every 2–3 months and lasting about 3 days. The last spontaneous menstruation was in 1943, and the cessation was accompanied by lassitude and occasional flushes.

She was of average height (176 cm.) and weight (58·2 kg.). Her breasts were underdeveloped and her external genitalia infantile. The vagina was small and the uterocervical canal measured 6 cm. The urinary gonadotrophin excretion was persistently high and the basal temperature recording was monophasic.

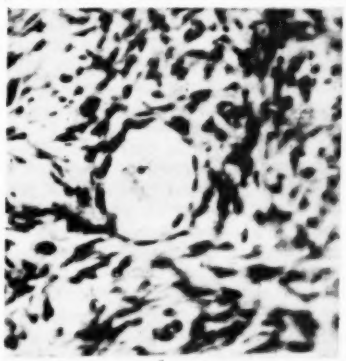

Fig. 2—Section of ovary showing primordial follicle.

Œstrogen therapy caused some development of the breasts and of the external genitalia, and also of the vagina and uterus, with slight uterine bleeding. But œstradiol implants of as much as 50 mg. induced only a limited response. The present appearance of the patient is shown in fig. 1.

At laparotomy in 1952 the ovaries

MARROW CHROMOSOME COUNTS

| — | Chromosome number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 44 | 45 | 46 | 47 | 48 | Polyploids | Total |
| Cells counted | 1 | 1 | 5 | 51 | 2 | 3 | 63 |

looked postmenopausal. Biopsy provided a wedge measuring 1 × 0·5 cm. in cross-section. On examination, the stroma appeared normal and contained only one primordial follicle (fig. 2); a later follicle with a granulose-cell layer was also seen, but no corpora albicantia were obvious. If this biopsy material is representative of the ovarian tissue as a whole, follicle formation has been deficient.

*Chromosome Analysis*

Sternal marrow was cultured and treated in the way described by Ford, Jacobs, and Lajtha (1958). The chromosomes of sixty-three cells were counted (see table).

The great majority of the cells contained 47 chromosomes, and departures from this number are attributed to artefacts arising during preparation. A detailed analysis was made of the chromosomes of thirteen cells of suitable quality. All were found to have an additional chromosome in the medium-size range where the X chromosome is to be found (fig. 3). It is presumed, therefore, that this patient has an XXX sex-chromosome constitution, and this presumption is supported by the findings on nuclear sex determination on buccal smears (see below) and by the fact that her abnormalities seem to be confined to the genital tract. The alternative explanation that the additional chromosome is an autosome is unlikely; for in mongolism, the only condition in which an additional autosome is known to occur, there are widespread abnormalities.

The skin was cultured by one of us (D. G. H.), and the chromosomes studied in forty-seven cells (Harnden 1959).

**Fig. 3—Representative marrow cell and idiogram showing 47 chromosomes and the presumptive X chromosomes.**

Of these, forty-three contained 47 chromosomes, two had 46 and two had 48. Deviations from 47 are thought to have occurred during culture or the preparation of the material for microscopy. Analysis of the chromosomes confirmed the bone-marrow findings.

Examination of the bone-marrow chromosomes of the mother showed a normal diploid number of 46 with a chromosomal sex of XX.

*Nuclear Sex Analysis*

Buccal smears were stained with cresyl echt violet (Moore and Barr 1955) and with thionin (Klinger and Ludwig 1957). By both methods sex-chromatin bodies were demonstrated in a high proportion of cells. In the smears stained with cresyl echt violet 57% of the nuclei contained a single chromatin body and 14% contained two chromatin bodies. In these latter cells there was some variation in the appearances of the bodies and in their positions on the nuclear membrane; in the majority the bodies were clearly separated (fig. 4A–C). Where a cell contained two chromatin bodies they did not differ significantly in size. In one cell, however, one of the bodies appeared in a " diplococcal " form (fig. 4C).

The proportion of cells containing chromatin bodies (71%) was greater than that found in buccal smears from normal women stained with the same preparation of cresyl echt violet. Twenty-five smears were obtained from 20 normal women, and

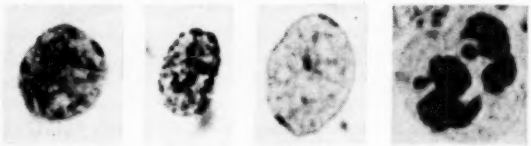


**Fig. 4—Cells from buccal mucosa and blood showing double sex-chromatin bodies.**

in each smear a hundred cells were examined. The percentage of chromatin-positive cells varied from 36 to 51, the mean value being 40·8 and the standard deviation 3·4. In none of these control preparations was a cell seen containing two chromatin bodies.

Female nuclear appendages were seen in the blood-films: 8 " drumsticks " (Davidson and Smith 1954) were present in five hundred neutrophil polymorphs, and 22 appendages—types A and B (Kosenow and Scupin 1956)—were observed in a further thousand neutrophils. The nuclear sex was clearly female, but the proportion of cells containing appendages was not in excess of that in normal women. Only one cell was found to contain 2 drumsticks (fig. 4D).

Sections of ovarian tissue were also stained with cresyl echt violet and with thionin, and in some of the stromal cells 2 chromatin bodies were seen.

## Discussion

It is now apparent that the condition can exist in man in which the chromosome number is 47, composed of 44 autosomes and 3 X chromosomes. This condition is analogous to the super-female found in *Drosophila melanogaster*. In this organism primary non-disjunction of the X chromosome occurs with a frequency of about 1/2000 (Waddington 1950), and eggs containing an XX pair when fertilised by X-bearing sperms give rise to super-females. In drosophila such super-females are often inviable. Our case suggests that in man the condition may affect only the genital tract.

Our finding that some of the cells of the buccal mucosa contain a second sex-chromatin body raises the possibility that the heterochromatic mass of the third X chromosome may be visible. This, however, seems unlikely; for, if it were so, the heterochromatic mass of the single X chromosome of the male should also be visible. The fact that the single X chromosome in the male is not visible suggests that the additional X chromosome in our case may contain an unusual amount of heterochromatic material. Only a more detailed study of further examples of this condition will decide whether this is the correct interpretation.

A further anomaly is the finding that the proportion of drumsticks in the polymorphonuclear leucocytes was no higher than in normal females. The significance of this observation, too, is not clear; but it does raise the possi-

bility the polymorphonuclear appendages are not such a direct indication of the presence of two X chromosomes as is the presence of a nuclear sex-chromatin body in buccal mucosal cells.

If it can be shown in further cases that the proportion of cells containing two chromatin bodies is associated with an XX chromomal sex, determination of the nuclear sex chromatin on buccal mucosal cells may be a valuable screening procedure in looking for the " super-female ".

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# CHROMOSOME STUDIES IN HUMAN LEUKÆMIA

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THE occurrence in neoplastic cells of chromosome abnormalities, both of number and form, is now well established, although their frequency and significance in relation to carcinogenesis remains uncertain (Levan 1956, Koller 1957). Recent technical advances have facilitated more accurate observations on human chromosomes, particularly those of marrow cells, and the karyotype has been studied in a number of cases of leukæmia. Previously Ford, Jacobs, and Lajtha (1958) had reported their findings in twelve cases of human leukæmia, in only three of which, however, was a complete analysis possible; in one of these, a blast-cell leukæmia, the karyotype was abnormal, but in the other two the chromosomes were normal in number and appearance. The need for further studies has been emphasised by the discovery that mongols are trisomic for one of the smallest acrocentric autosomes (Lejeune, Gauthier, and Turpin 1959, Jacobs, Baikie, Court Brown, and Strong 1959), and by the reported association between their particular trisomic state and a raised mortality from childhood leukæmia (Carter 1956, Krivit and Good 1956, Stewart, Webb, and Hewitt 1958). Furthermore, leukæmia provides a special opportunity for serial chromosomal studies which may permit correlation of chrosomal abnormalities with the clinical type and behaviour of the disease, and may also shed light on the reasons for the variable response to treatment and for relapses after an initial response to chemotherapy.

We are now able to report the results of such serial chromosome studies in a case of acute leukæmia during the 8 months which elapsed between diagnosis and death. More limited observations have been made in eleven other cases of leukæmia and in two cases of myelomatosis.

## Material and Methods

Bone-marrow samples for chromosome analysis and for smear preparations were obtained by aspiration through a Salah needle. The chromosome studies on marrow material were carried out by the method described by Ford et al. (1958), and on the skin-biopsy material by the method of Harnden (1959). The hæmatological methods used were essentially those described by Dacie (1956), but bone-marrow was examined in smear preparations (Davidson, Davis, and Innes 1943) and defibrinated blood was used for buffy-coat films.

## Case-reports

In this section data are presented on cases 1–11 of leukæmia, and cases 12–13 of myelomatosis. Both the clinical and chromosomal data are presented in full for case 1, and are summarised (table II) for the remaining cases.

**Case 1.**—A woman, aged 56, was admitted to hospital in August, 1958. For 4 weeks she had been unduly tired, and she had had a severe epistaxis. There were no notable features in her medical history, and at no time before her final illness was she exposed to artificial radiation. She was pale, and had a few retinal hæmorrhages. Clinically there was no enlargement of liver, spleen, or lymph-nodes.

Her blood and marrow were examined on Sept. 3, at which time marrow chromosome studies were also undertaken. The blood findings were: Hb 4·6 g. per 100 ml.; packed-cell volume 15%; platelets 78,000 per c.mm.; reticulocytes 0·6%, white-cell count 1700 per c.mm. (polymorphs 35%, lymphocytes 50%, abnormal mononuclears 15%).

The abnormal mononuclear cells varied in size and apparent maturity, but most had the characteristics of primitive cells. Similar mononuclear cells predominated throughout the bone-marrow, and here they were generally larger and more immature. Erythropoiesis was normoblastic and few megakaryocytes were seen. A diagnosis of acute aleukæmic leukæmia was made, and the leukæmic cells were thought to be of the myelomonocytic variety.

*Course of Illness*

Treatment was by initial blood-transfusion and prednisolone 60 mg. daily, which was reduced to 40 mg. daily before her discharge from hospital on Sept. 19. On this regime the white-cell count rose and was maintained between 8000 and 10,000 per c.mm., the differential count remaining unchanged. The platelet-count varied between 90,000 and 120,000, but the hæmoglobin level declined slowly and the patient was re-admitted for a further blood-transfusion on Dec. 8. The dose of prednisolone was increased to 60 mg. daily, and thereafter the hæmoglobin level was maintained without further transfusion. On Oct. 15, and again on Jan. 5, 1959, the bone-marrow biopsy was repeated for routine hæmatology and for chromosome counts.

In February, 1959, a rib fractured. There was no evidence of a generalised osteoporosis, but other steroid side-effects were by now conspicuous. She felt less well and purpuric spots appeared frequently, although both platelet and hæmoglobin levels were maintained at the previous improved figures (Hb 11·4 g. per 100 ml., platelets 110,000 per c.mm.), and the white-cell count was essentially unchanged (7600 per c.mm.).

She was readmitted to hospital in March, so that the dose of prednisolone might be reduced under observation. Radiography showed two more rib fractures. Although the dose of prednisolone was slowly reduced and corticotrophin was substituted, the levels of hæmoglobin, platelets, and white cells fell rapidly. This hæmatological deterioration continued, and 2 days after the last dose of corticotrophin the patient had hæmaturia and rectal bleeding. Steroid therapy was resumed, using dexamethasone 6 mg. daily, and thereafter the hæmoglobin, platelet-counts, and white-cell counts all rose to their previous levels and the patient became fit to return home. Bone-marrow biopsy was repeated on April 2, and although the appearance of the smears was substantially unaltered there now was a marked change in the chromosome constitution of the cells.

On April 7 the patient was readmitted for the last time. She

TABLE I—CHROMOSOME COUNTS IN CASE 1

| Marrow sample | Date | Site | Chromosome number | | | | | | | | | | | | | Cells counted |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | <43 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | >50 | 4N | 8N | >8N | |
| A | Sept. 3, 1958 | Sternum | 2 | .. | 3 | 2 | 24(8)* | 45 | 75 | 27 | 6 | .. | .. | .. | .. | 184 |
| B | Oct. 15, 1958 | Sternum | .. | 1 | 1 | 1 | 12(5) | 25 | 28 | 9 | 1 | .. | 1 | .. | 1 | 80 |
| C | Jan. 5, 1959 | Sternum | .. | 1 | .. | 2 | 9(2) | 25 | 46 | 15 | 4 | 1 | 1 | .. | .. | 104 |
| D | April 2, 1959 | Sternum | .. | .. | 1 | 2 | 9(7) | 34 | 22 | 12 | 1 | .. | 2 | 1 | .. | 84 |
| E | April 20, 1959 | Sternum | .. | 1 | .. | 2 | 7(4) | 36 | 25 | 15 | 8 | 1 | 5 | .. | .. | 100 |
| F | „ „ „ | Lumbar spine | .. | .. | 1 | 1 | 4(1) | 7 | 9 | 13 | 3 | 1 | .. | .. | .. | 39 |
| G | „ „ „ | Iliac crest | .. | .. | .. | 3 | 5(2) | 18 | 20 | 6 | 1 | 7 | 2 | 1 | .. | 63 |

* Numbers in parentheses indicate the number of cells with a diploid number of 46 in which no morphological abnormalities could be seen.

$\chi^2$ *tests.*—For this purpose the polyploid cells were ignored and the remaining numbers were grouped as follows: $\leqslant$46, 47, 48, 49, $\geqslant$50

Results: comparison of B with A, $\chi^2=2{\cdot}20$; $P>0{\cdot}50<0{\cdot}70$; C with A+B, $\chi^2=3{\cdot}42$, $P>0{\cdot}30<0{\cdot}50$; D with A+B+C, $\chi^2=9{\cdot}58$; $P>0{\cdot}02<0{\cdot}05$; D+E with A+B+C, $\chi^2=16{\cdot}64$, $P<0{\cdot}01$; F with E, $\chi^2=8{\cdot}18$, $P<0{\cdot}05>0{\cdot}10$.

complained of severe back pain, and there was radiological evidence of erosion of the bodies of L1–3 but no evidence of generalised decalcification. The bone lesions were thought to be due to leukæmic infiltration, and palliative radiotherapy was given to the lumbar vertebræ. A single surface dose of 1000 rads was given to a 15 × 10 cm. field centred posteriorly over the spinous process of L2. After this, there was a slight fall in her blood-levels to Hb 9 g. per 100 ml., platelets 83,000 per c.mm., and white cells 4400 per c.mm. On April 20 she collapsed suddenly with signs of massive gastro-intestinal-tract hæmorrhage, and died despite blood-transfusion. Immediately after death, bone-marrow was aspirated from the sternum, iliac crest, and the spinous process of the first lumbar vertebra. These marrow samples were used for further examination of the marrow-cell chromosomes as well as for conventional smear preparations.

*Postmortem Findings*

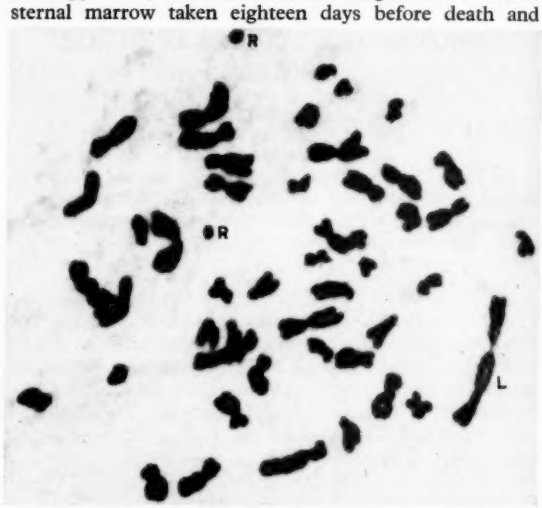
The histological appearances on the bone-marrow accorded with those of these smear preparations. There was no leukæmic infiltration, other than a few cells in the spleen and in a mesenteric lymph-node. The bone lesions noted in life were seen to be due to osteoporosis and not to leukæmic infiltration. The adrenal cortex showed marked atrophy, and there was severe fatty change in the liver.

*Comment*

Apart from the abnormality of the bone-marrow chromosomes, other notable features of this case of acute myelomonocytic leukæmia were persistence of the relatively aleukæmic peripheral blood-picture, and the small amount of infiltration of other organs compared with the bone-marrow. The evidence of leukæmia in marrow and peripheral blood was unaltered by steroid therapy. In this case steroids apparently helped by sustaining production and survival of red cells and by maintaining hæmostasis.

## Chromosome Studies

The chromosome-counts done on sternal marrow obtained from case 1 on five times in eight months were all abnormal (table I). On the first three occasions they ranged from 46 to 50, with a well-defined modal number of 48, and there were ring chromosomes (often positively heteropyknotic) and chromosome fragments. In the sternal marrow taken eighteen days before death and immediately after death the modal chromosome number had changed to 47. Ring chromosomes and fragments were still present, and in addition an abnormally large submetacentric chromosome was seen in three cells (see figure). The marrow from the lumbar vertebra, which had been irradiated 5 days before death, contained considerably fewer cells in mitosis than did the sternal




**Cell from bone-marrow showing 50 chromosomes. R, ring chromosome. L, large submetacentric chromosome.**

TABLE II—DETAILS OF PATIENTS STUDIED

| Case | Age | Diagnosis | Date (1959) | Whether treated | Chromosomes | |
|---|---|---|---|---|---|---|
| | | | | | No. | Structural abnormalities |
| 2 | 64 | Acute leukæmia | May 14 | Untreated | 46–50 | None seen |
| | | | June 2 | Treated | 46–50 | „ „ |
| 3 | 41 | Acute leukæmia | Jan. 5 | Treated | 46 | Probable translocation |
| | | | Jan. 19 | „ | 46 | „ „ |
| | | | Feb. 10 | „ | 46 | „ „ |
| 4 | 48 | Acute leukæmia | May 8 | Untreated | 46 | Probable translocation |
| | | | May 26 | Treated | 46 | „ „ |
| 5 | 70 | Acute leukæmia, polycythæmia vera | .. | Treated | 46 | None |
| 6 | 50 | Chronic myeloid leukæmia | .. | Treated | 46 | None |
| 7 | 76 | Chronic myeloid leukæmia | .. | Untreated | 46 | None |
| 8 | 61 | Chronic myeloid leukæmia | .. | Untreated | 46 | None |
| 9 | 72 | Chronic myeloid leukæmia | .. | Treated | 46 | None |
| 10 | 51 | Chronic myeloid leukæmia | .. | Treated | 46 | None |
| 11 | 76 | Chronic lymphatic leukæmia | .. | Treated | 46 | None |
| 12 | 58 | Myelomatosis | .. | Untreated | 46 | None |
| 13 | 55 | Myelomatosis | .. | Untreated | 46 | None |

marrow removed at the same time; and the modal number was 49 in contrast to that of the unirradiated sternal marrow. In all marrow specimens there was a small proportion of cells having 46 chromosomes, but most of these contained chromosomes with structural abnormalities and cannot therefore be regarded as normal marrow cells.

To ascertain whether or not this patient had an inherent chromosome abnormality a skin biopsy was performed on April 7. The specimen of skin was cultured (Harnden 1959), and the chromosomes were examined. In thirty-six of the thirty-seven cells analysed the chromosome number was 46 and there were no morphological abnormalities. Variation from this number was attributed to the culture technique.

Preliminary results of chromosome studies of the bone-marrow cells from ten further cases of leukæmia are shown in table II. In cases 5–11 the chromosomes numbered 46 and their morphology appeared normal. The material from case 2 yielded very few dividing cells, but in the twenty-one cells examined the chromosome number ranged from 46 to 50. In cases 3 and 4 the chromosome number was 46, but in both instances an abnormal chromosome was seen in a high proportion of the cells, the appearances of this chromosome suggesting that a translocation had given rise to an aberrant cell line.

## Discussion

The finding of chromosomal abnormalities in four out of five cases of acute leukæmia, and the apparent absence of such changes in six cases of chronic leukæmia and two of myelomatosis raises two interdependent problems. What is the relation of these chromosome changes to the pathogenesis of acute leukæmia, and does their absence in chronic leukæmia denote an essential difference between the acute and chronic forms, either in their mechanisms of induction or in their pathogenesis? Three possibilities may be considered. Firstly the chromosome changes may arise as epiphenomena in a grossly disordered bone-marrow; secondly the visible chromosome changes may include the fundamental change which has conferred neoplastic qualities on the marrow cells; and thirdly it is possible that the chromosome changes are the consequences —perhaps the remote consequences—of a more subtle alteration in the genetic constitution of the leukæmic cell. This last interpretation seems the most likely.

If the chromosome changes arise merely as a result of a gross disorder of the bone-marrow, it is difficult to understand why none have been found in the chronic leukæmias, in which the marrow was at least as disordered as in many instances of acute leukæmia, and perhaps more so than in cases 1 and 3. It is possible that translocations, such as would account for the findings in cases 3 and 4, were also present in cases 1 and 2 but were obscured by the more gross changes present; and it could be that such translocations represent the fundamental structural change which induces leukæmia. On the other hand it may well be that the gross and varied chromosome changes found in four of our cases, and in the single case of Ford et al. (1958), arose as the consequence of a more subtle genetic change which is not demonstrable by current techniques.

Thus our observations appear to strengthen the concept that acute leukæmias are the result of changes in the genetic material in the cell. On the other hand they throw no further light on the induction mechanisms of the chronic leukæmias. Possibly separate mechanisms of induction and of development exist for chronic myeloid and chronic lymphatic leukæmia. Thus the incidence of chronic lymphatic leukæmia is apparently unaffected by radiation exposure, whereas that of chronic myeloid leukæmia is raised, along with the incidence of the acute forms of leukæmia. Furthermore, from an analysis of death-certificate data, Court Brown and Doll (1959) have inferred that chronic lymphatic leukæmia may have a separate ætiology from the other two types. As only one case of chronic lymphatic leukæmia has been examined by us, the remainder of this discussion relates only to the acute leukæmias and to chronic myeloid leukæmia.

Armitage and Doll (1957) have suggested that cancer induction is a staged process, and that the first stage consists of a change in the genetic structure of the cell. The nature of the later stages remains obscure, but possibly further genetic changes occur in a random fashion, and an autonomous state ultimately develops. On this hypothesis our findings may imply that in chronic myeloid leukæmia the fundamental change allows the affected cell series to escape from the usual factors which regulate cell replacement; at the same time cell differentiation continues along roughly normal lines, and genetic changes are limited. The converse may be true of acute leukæmia, where the rate of cell replacement may be little affected, but where departures from normal cell differentiation are marked, and progressive chromosomal aberrations are possible. Certainly the heterogeneity of chromosome number and form in the bone-marrow of case 1, and their progressive changes, provide a rationale for the natural history of acute leukæmia and its response to treatment. Moreover on this basis both the escape of acute leukæmia from the control of initially effective treatment, and the failure of some cases to respond at all, can be understood.

In case 1 it is noteworthy that the limited effects of steroids produced no change in the chromosome constitution and little or none in the hæmatological evidence of leukæmia. It is also of interest that the bone-marrow taken after death from the lumbar vertebra, which had been directly irradiated, showed a different modal chromosome number—although this difference is only on the borderline of statistical significance. This suggests that the cell line with a chromosome number of 47, which had become predominant, may have been especially radiosensitive. Whether this interpretation is justified or not, it is obvious that these methods provide an opportunity for the examination of the chromosome constitution of leukæmic cells—an opportunity which may be expected to give new insight into the natural history of the disease, whether treated or untreated, and perhaps into its fundamental nature.

## Summary

A case of acute leukæmia is described in which the bone-marrow cells had a modal chromosome number of 48, as well as abnormalities of chromosome form. Serial observations showed that during treatment with steroids all these abnormalities persisted until seven months after diagnosis when the modal chromosome number changed to 47.

The bone-marrow chromosomes of four other cases of acute leukæmia were examined: one had an abnormality of chromosome number and two had morphological abnormalities alone. In contrast, no chromosomal abnormalities were found in six cases of chronic leukæmia, or in two cases of myelomatosis.

These findings are discussed in relation to the pathogenesis of leukæmia; and in relation to the natural history of acute leukæmia and the effects of treatment.

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# STAPHYLOCOCCAL PNEUMONIA IN INFLUENZA

## IN RELATION TO ANTECEDENT STAPHYLOCOCCAL SKIN INFECTION *

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DESPITE powerful antibiotics, secondary bacterial infection was still the most important single or accessory cause of death in the influenza pandemic of 1957–58; and *Staphylococcus aureus* was the most common offender (Public Health Laboratory Service 1958, Hers et al. 1958). In order to reduce the death-rate of influenza the prevention and treatment of this complication must therefore be one of the most important points of attack. Prevention requires a better understanding of the epidemiological pathways of the staphylococcus: improvements in therapy must include the use of the right antibiotic from the start and the early treatment of toxæmic shock.

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### Materials and Methods

In this investigation all but one of the strains of staphylococci were isolated from the sputa or postmortem material of cases in which the diagnosis of Asian influenza had been established by virological methods. Since Stokes and Wolman (1940) and Mulder (1952) have reported antecedent staphylococcal skin lesions in patients with influenza and secondary staphylococcal pneumonia, or in members of such patients' families, all patients, their relatives, and their close contacts have been questioned with this possibility in mind. The same was done in all patients admitted to the department of pædiatrics of the University of Leiden and the department of medicine of the Municipal Hospital, Dordrecht. Furthermore we received material and data from various cases from other parts of the country. If skin lesions were still present, the causative staphylococcus was cultured, kept, and compared with the strain from the respiratory tract. If the lesions had already healed, a swab was taken from the nose and cultured for staphylococci, on the assumption that nasal strains are often identical with those causing skin lesions (Hobbs and Carruthers 1947, Valentine and Hall-Smith 1952, Tulloch 1954). All strains were tested for coagulase activity and for sensitivity to the commonly used antibiotics (Hoette and Struyk 1958); and later they were phage-typed by the method of Williams and Rippon (1952).

TABLE I—DISTRIBUTION OF ANTECEDENT STAPHYLOCOCCAL SKIN LESIONS IN PATIENTS, MEMBERS OF THEIR FAMILIES, AND OTHER CONTACTS IN STAPHYLOCOCCAL PNEUMONIA ASSOCIATED WITH INFLUENZA

| — | Total numbers | Patient | Family | Other contacts |
|---|---|---|---|---|
| Proven cases .. | 25 | 9* | 17* | 2 |
| Probable cases.. | 3 | 0 | 3 | 0 |
| Possible cases .. | 26 | 7 | 19 | 0 |
| Total .. | 54 (*100%*) | 15 (*28%*) | 39 (*72%*) | 2 (*4%*) |

* In 3 cases a skin lesion was present in the patient as well as in a member of the family.

TABLE II—STAPHYLOCOCCAL PNEUMONIA ASSOCIATED WITH INFLUENZA IN RELATION TO ANTECEDENT STAPHYLOCOCCAL SKIN LESIONS IN THE PATIENT OR IN HIS SURROUNDINGS

| Patient | H.I. test (paired sera) | Staphylococcus from sputum | | | | | | Staphylococcus from skin lesion | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Antibiotic sensitivity | | | | | Phage type | Type of skin-lesion | Relation to patient | Antibiotic sensitivity | | | | Phage type |
| | | P | S | C | T | E | | | | P | S | C | T | E | |
| A. Youth of 17 admitted 3rd day of illness | <9/4608 | + | + | + | + | + | −/No*/52 | Folliculitis of face | Patient himself | + | + | + | + | + | −/No/52 |
| B. Youth of 18 admitted 17th day | 151/480 | + | + | + | + | + | −/29/− | Infected knee wound | Brother | + | + | + | + | + | −/29/− |
| C. Girl of 17 admitted 12th day | 256/64 (12th day) (60th day) | + | + | + | + | + | 70,29/No/+ | Acute furunculosis | Man nursed by patient | + | + | + | + | + | 70,29/No/+ |
| D. Youth of 16 admitted 3rd day | <9/13031 | − | + | + | + | + | −/29,No/− | Acute furunculosis | Patient | − | + | + | + | + | −/29,No/− |
| E (brother of D). Aged 19, admitted 6th day | <9/914 | − | + | + | + | + | −/29,No/− | Acute furunculosis | Brother | − | + | + | + | + | −/29,No/− |

* No=phage adapted by ourselves from phage 42 E, almost but not entirely identical with phage 80.
P=penicillin. S=streptomycin. C=chloramphenicol. T=tetracycline.
E=erythromycin. H.I. test=hæmagglutination inhibition test.

TABLE III—FREQUENCY OF SECONDARY STAPHYLOCOCCAL INFECTION IN VIRAL INFLUENZA WITH ANTECEDENT STAPHYLOCOCCAL SKIN INFECTION IN THE PATIENT OR IN HIS SURROUNDINGS

| Hospital | Year | Cases admitted | Antecedent staphylococcal skin lesion | | | | | No antecedent lesion |
|---|---|---|---|---|---|---|---|---|
| | | | Proven* correlation | Probable† correlation | Possible‡ correlation | Total correlation | Negative§ correlation | |
| Department of Medicine, Leiden | 1956 | 3 | 2 | 0 | 0 | 2 | 0 | 1 |
| | 1957 | 14 | 5 | 1 | 1 | 7 | 2 | 5 |
| | 1958 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| Department of Pædiatrics, Leiden | 1957 | 11 | 2 | 0 | 4 | 6 | 0 | 5 |
| Department of Medicine, Municipal Hospital, Dordrecht | 1957 | 11 | 4 | 0 | 2 | 6 | 0 | 5 |
| Total .. .. .. .. .. | | 40 (100%) | 14 (35%) | 1 (2·5%) | 7 (17·5%) | 22 (55%) | 2 (5%) | 16 (40%) |

* Strain from skin lesion cultured and identical with strain from sputum or postmortem material.
† Strain from nose-swab identical with strain from sputum or postmortem material.
‡ Only history of antecedent staphylococcal skin lesion; no strain cultured.
§ Strain from skin lesion cultured and different from strain from sputum or postmortem material.

## Results

### *Correlation between Skin and Lung Infection*

In 57 patients or close contacts a staphylococcal skin lesion was still active or had been active until shortly before the staphylococcal pneumonia. In 25 of these the strain from the skin lesion was identical with the strain cultured from the sputum or postmortem material; and, in 3 in whom the skin lesion had already healed the staphylococcus from the nose-swab was identical with the respiratory strain. In 3 cases different strains were isolated.

In 26 cases with a history of staphylococcal skin infection we could not isolate and identify the causative strain: the usual reason for this was that the postmortem examination was performed in some other part of the country; and information did not reach us in time. It seems reasonable to assume, however, that in this group the proportion of those in whom the skin or nasal and the respiratory strains were identical was similar to the 31 fully investigated cases.

We found only about a third of the skin lesions in the patients themselves: most were in members of their families; and in 2 cases the infection was transmitted to a nurse (table I). Overt lesions were by far the commonest: acute furunculosis was present in 38 cases, folliculitis in 7, superficial pyodermia in 4, chronic otitis media in 2, hordeolum in 1, and infected skin wounds in 6 (table II). Sometimes more than one lesion was present.

The frequency of the correlation in 40 cases is set out in table III.

### *Sensitivity and Phage Type*

It was soon apparent that strains from the sputa or postmortem material of cases who had been in hospital for a few days differed in sensitivity and phage type from strains obtained on admission or from necropsies performed within twenty-four hours of admission. Our cases were divided accordingly into two groups (table IV). Although in the first-day group about a third of cases were resistant to penicillin and a tenth to streptomycin, a very few were resistant to other antibiotics. Cultures taken on later days—especially of postmortem material—showed not only an increase in resistance to penicillin and streptomycin but also many more strains resistant to other antibiotics (table IV).

TABLE IV—SENSITIVITY OF STAPHYLOCOCCI ISOLATED FROM CASES OF ASIAN INFLUENZA WITH SECONDARY STAPHYLOCOCCAL INFECTION

| — | Strains from sputum | | Strains from post-mortem material | |
|---|---|---|---|---|
| | Within a day of admission | Later days | Within a day of admission* | Later days † |
| Total .. .. | 61 (100%) | 12 (100%) | 52 (100%) | 39 (100%) |
| Penicillin-sensitive | 42 (69%) | 6 (50%) | 32 (62%) | 10 (26%) |
| Penicillin-resistant | 19 (31%) | 6 (50%) | 20 (38%) | 29 (74%) |
| Streptomycin-resistant | 5 (9%) | 4 (33%) | 5 (9%) | 20 (51%) |
| Chloramphenicol-resistant | 0 | 1 (8%) | 1 (2%) | 5 (13%) |
| Tetracycline-resistant | 0 | 3 (25%) | 2 (4%) | 11 (28%) |
| Erythromycin-resistant | 0 | 0 | 0 | 3 (8%) |

* 1 case yielded two different strains.
† 7 cases showed two different strains, 1 case three different strains.

TABLE V — DISTRIBUTION OF PHAGE GROUPS AND TYPES IN STAPHYLOCOCCI ISOLATED FROM CASES OF ASIAN INFLUENZA

| — | Strains from sputum | | Strains from post-mortem material | |
|---|---|---|---|---|
| | Within a day of admission | Later days | Within a day of admission† | Later days‡ |
| Total .. .. | 60 (100%) | 12 (100%) | 52 (100%) | 39 (100%) |
| Group I .. .. | 22 (37%) | 3 (25%) | 18 (35%) | 7 (18%) |
| Group II .. .. | 8 (15%) | 0 | 7 (12%) | 3 (8%) |
| Group III .. .. | 2 (4%) | 3 (25%) | 3 (5%) | 10 (26%) |
| 80/No .. .. | 12 (20%) | 4 (33%) | 9 (17%) | 7 (18%) |
| 44B * .. .. | 3 (5%) | 0 | 7 (13%) | 3 (8%) |
| 187 .. .. .. | 4 (7%) | 1 (8%) | 0 | 0 |
| N.S. .. .. .. | 3 (5%) | 1 (8%) | 3 (6%) | 0 |
| N.T. .. .. .. | 6 (11%) | 0 | 5 (9%) | 9 (23%) |

* Adapted by ourselves from phage 44.
† 1 case yielded two different strains.
‡ 7 cases showed two different strains; 1 three different strains.

The two groups also differed in phage type, the most important difference being the considerable increase in group-III strains, after the first day in hospital (table V).

## Discussion

The correlation, in influenza, between secondary staphylococcal infection and antecedent staphylococcal skin lesion seems too close to be fortuitous. It is true that no series of influenza patients with secondary infection by other organisms has been examined for such a correlation; but in a somewhat similar series of pneumococcal infection no case showed antecedent staphylococcal infection.

We do not know what the likelihood of a staphylococcal respiratory infection is in somebody living in a family with an active staphylococcal lesion. A 100% correlation can never be expected. The development of a staphylococcal infection in influenza might be determined by at least two factors. First there is the degree of cellular damage by the virus (just as a third-degree burn is more liable to secondary infection than a first-degree one): this would explain the comparative rarity of

secondary staphylococcal pneumonia in influenza patients in contact with staphylococcal lesions. Secondly, the virulence of the staphylococcus as it crosses the epidemiological path of the virus is undoubtedly important. Virulent staphylococci do not always show themselves by active skin lesions—as the high proportion of patients and hospital staff who carry virulent hospital staphylococci shows—but an active lesion is a warning signal that such an organism is circulating. It seems wise to heed this signal in time of influenza and to treat all staphylococcal lesions, especially furunculosis, with the utmost care. If a member of a family which harbours the staphylococcus contracts influenza the patient should be watched carefully for any sign of secondary infection and treated from the beginning or even prophylactically with the right antibiotic.

The change in staphylococcal sensitivity while patients are in hospital might be explained by acquired resistance were it not for the lack of correlation between acquired resistance and therapy and for the coincidental change in phage pattern. Preagonal aspiration from the nasopharynx of resistant staphylococci acquired in hospital cannot account for the change of organism in patients' sputa.

The relative importance of secondary superficial contamination of the bronchial tree cannot be accurately assessed. It is true that in some postmortem cases a resistant strain was cultured only from the trachea, while the strain from the pneumonic material was fully sensitive; but often the material from both trachea and lung tissue yielded a resistant strain. The proven fact that resistant staphylococci acquired by influenza patients in hospital can descend into the bronchial tree may well influence the outcome of the pneumonic process. This makes it necessary to culture the sputum of influenza patients with secondary staphylococcal pneumonia repeatedly, if possible every day, after admission.

**Summary**

We investigated 40 cases of influenza with secondary staphylococcal pneumonia for a possible antecedent staphylococcal skin or other open lesions. In 14 cases (35%) correlation could be proved by the similarity between the causative organism of the skin lesion and the pneumonia: in a further 8 cases (20%) such a correlation appeared probable. A proven or probable correlation was found in another 32 cases from various hospitals in the country.

Appreciation of these facts in the management of patients may lead to a diminished incidence of staphylococcal infection in influenza.

Resistance to antibiotics increased after admission; and phage typing showed a considerable increase of group-III strains in cultures isolated after the first twenty-four hours.

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# OSTEOCHONDRODYSTROPHY (MORQUIO'S DISEASE) IN THREE GENERATIONS

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OSTEOCHONDRODYSTROPHY is a developmental defect of the skeleton which may result in almost complete arrest, or any degree of partial arrest, of ossification of cartilage. The whole skeleton may be affected to a variable extent, with the exception of the skull and face which remain normal. In some cases the dystrophy is so slight that it escapes detection, while in others it results in dwarfism and deformity.

**Fig. 1—Lumbar spine showing flattened irregular vertebræ with Schmorl's nodes and calcification of the intervertebral discs.**

The earliest adequate description of this hereditary and familial condition was given by Morquio (1929), and the radiological changes were described in detail by Brailsford in the same year.

Morquio described 4 cases among 5 siblings with a history of consanguinity both of parents and of paternal grandparents. Of the 2 siblings reported in detail, both had normal skulls and no gross radiological abnormality of the spine beyond scoliosis and spina bifida. In the limbs there was marked deformity of both humeral and femoral heads, and the epiphyses at the elbow and knee joints were also deformed. Many of the long bones were curved, shortened, and unequal in length. Ossification was absent from the carpal bones and incomplete in the tarsus. Shortening, broadening, and deformity of the metacarpals, metatarsals, and phalanges were prominent features.

Over 100 cases of Morquio's disease have now been reported—mostly isolated or in siblings. Jacobsen (1939) described 20 cases in five generations, the condition being strictly recessive, sex-linked, and transmitted through normal daughters to half their sons. In 1 case transmission was through three generations of normal females. Gates

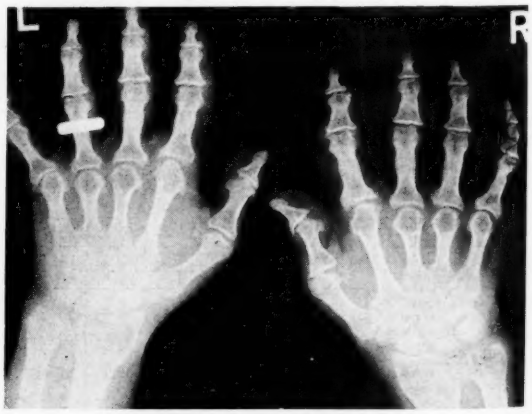


**Fig. 2—Malformed carpal bones, and short broad malformed metacarpals and phalanges.**

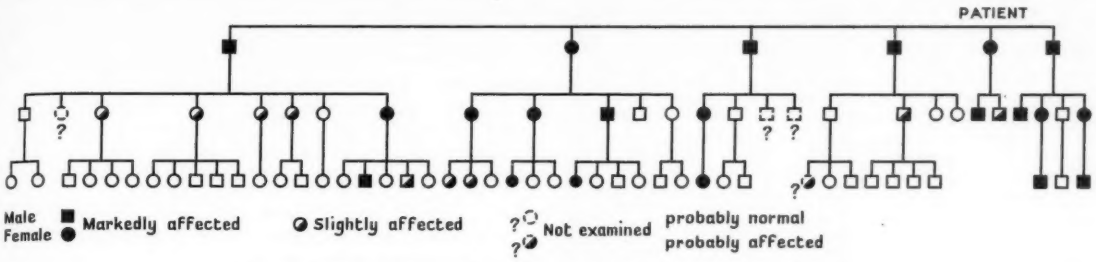


**Fig. 3—Family tree showing three generations affected by Morquio's disease.**

(1946) stated that the condition may be transmitted as a mendelian dominant in certain families, while Shelling (1947) was of the opinion that a dominant factor may be involved; but in all published cases the hereditary trait appears as a mendelian recessive.

## Present Study

*The Propositus*

A woman aged 57 attended the outpatient department complaining of pain and stiffness in many joints, principally in the hips and knees. On examination she was just over 4 ft. tall with marked kyphosis and stiffness of the spine. The hips showed some flexion deformity with restricted movement. Movement of the shoulders was also restricted, and there was gross crepitus in both knees. The hands were short and spatulate.

X-ray examination of the spine (fig. 1) showed typical flattened, irregular, shallow vertebræ with advanced dorsal kyphosis, and calcification of the intervertebral discs with Schmorl's nodes. The hands (fig. 2) showed wide joint spaces between malformed carpal bones and short broadened and deformed metacarpals and phalanges, with secondary degenerative changes in the joints. The hips showed flattened acetabula with shortening and thickening of the femoral necks and gross secondary osteoarthritic changes.

*Heredity*

Of a total of 79 members in three generations of the patient's family all but 4 were examined. Evidence of osteochondrodystrophy was found in 31—18 females and 13 males (fig. 3). All grades of osteochondrodystrophy were found, from minor changes involving only the metacarpals, the phalanges, or an isolated vertebra, to the florid picture as described by Morquio.

The disease has been transmitted as a mendelian recessive factor to both sexes through affected males and females with diminishing frequency and severity. All members of the first generation, 55% of the second generation, and 22% of the third generation were affected. None of those with minor involvement transmitted the condition, which thus tended to die out in succeeding generations.

DISTRIBUTION OF RADIOLOGICAL CHANGES

| Generation | Case no. | Hands | Dorsal spine | Lumbar spine | Pelvis |
|---|---|---|---|---|---|
| 1 | 1 | − | + + | + + | — |
| | 2 | + + | + + | + + | + + |
| | 3 | + + | + + | + + | + + |
| | 4 | + | — | + + | — |
| | 5 | + + | + + | + + | + + |
| | 6 | + + | + + | + + | + |
| 2 | 7 | + + | + | + | — |
| | 8 | + | — | — | — |
| | 9 | + | — | — | — |
| | 10 | + | — | — | — |
| | 11 | + | — | + | — |
| | 12 | + + | + + | + + | + |
| | 13 | + + | + + | + + | + |
| | 14 | + + | + + | + + | — |
| | 15 | + + | + + | + + | + |
| | 16 | + + | + + | — | + + |
| | 17 | + + | + | + | — |
| | 18 | — | + | + | — |
| | 19 | + + | + + | + + | + |
| | 20 | + + | + + | + + | — |
| | 21 | + + | + + | + + | + |
| 3 | 22 | + | — | + | — |
| | 23 | + + | + | — | — |
| | 24 | + | — | + | — |
| | 25 | + | + | + | — |
| | 26 | + | + | — | — |
| | 27 | + + | + + | + | — |
| | 28 | + + | + + | + | + |
| | 29 | + | — | — | — |
| | 30 | + + | + + | + + | + |
| | 31 | + + | + | + | + |

+ + = Severely affected. + = Slightly affected. — = Not affected.

**Fig. 5—Involvement of a single vertebra.**

**Fig. 4—Spine showing anterior tongue-like projections of vertebral bodies.**

*Radiological Changes*

In all cases X-rays were taken of the hands, dorsal and lumbar spines, and pelvis. In the first generation, all 6 patients were severely affected. Of 27 in the second generation, 15 were affected; and 9 of these had major involvement of the skeleton. Of 45 in the third generation, 5 were severely affected; and 5 had minor changes.

*Distribution.*—This is shown in the table. In all except 1 case (97%) X-ray evidence of the disease could be detected in the hands: those least affected most commonly had changes in either the fourth or the fifth metacarpal.

The dorsal and lumbar spine was affected in 74% and 77% of cases respectively. Changes in the pelvis were much less common (45%), the least involvement being represented by an abnormal pelvic contour or deformity of the femoral heads.

*Vertebral column.*—The vertebral bodies vary in size and shape, causing lack of alignment of the column. Many vertebræ appear widened and flattened. In the lateral view there is commonly a defect in the upper margin of some of the bodies; this gives the impression that the lower margin projects forwards to form a hook. In other cases there is a defect in both upper and lower margins, resulting in an anterior tongue-like

projection of the middle of the affected vertebræ (fig. 4). Defective development of the articular processes may cause displacement of the vertebræ in the lumbodorsal region. At first the intervertebral discs may be thicker than normal; but in later life the spaces become narrower; and irregularity of the margins of the vertebræ is associated with changes in the disc plates and subchrondral bone (Campbell Golding 1950). Mildly affected members showed early calcification of the vertebral plates and intervertebral discs anteriorly, or sometimes involvement of a single vertebra only (fig. 5).

**Fig. 6—Knee-joint showing wide joint space and absence of tibial spines.**

*Long bones.*—The shafts are widened and shortened, especially at the diaphyseal ends, which may be irregular (fig. 6). Brailsford (1953) pointed to the large gaps between the bony extremities of the joints as an important feature. Osteoporosis and pressure deformities may occur, and joint surfaces such as the glenoid fossa or acetabulum may be flattened and irregular.

*Hands.*—Typically these are short and spatulate due to broadening and shortening of the metacarpals and phalanges. The joint spaces tend to be widened, and failure or incomplete development of the carpus may lead to disorganisation of the wrist-joint.

*Other findings* included Paget's disease of the pelvis (1 case), congenital dislocation of one hip with osteochondrodystrophy of the other (1 case), osteochondritis of the dorsal spine (1 case), and Madelung's deformity of both wrist-joints (1 case).

**Fig. 7—Slight involvement of the hands: a short fifth metacarpal.**

*Biochemical Features*

Investigations were confined to the 6 members of the first generation (all severely affected): all had a normal serum-calcium, serum-inorganic-phosphorus, and serum-alkaline-phosphatase.

### Discussion

At the outset of this study we wondered whether we should discover an explanation for the not uncommon variety of bilateral osteoarthritis of the hip which is not uncommonly seen in young patients who have no obvious primary cause. It seemed possible that they might be very mild cases of osteochondrodystrophy in whom secondary osteoarthritic changes would certainly supervene at an early age. The present study does not support this hypothesis, for in all cases in which the pelvis or femora was affected, marked changes were also seen in either the hands or the vertebral column.

Apart from the routine X-rays of hands, spine, and pelvis, each patient was questioned as to joint symptoms elsewhere: and osteochondrodystrophy with secondary osteoarthritic change was discovered in 5 shoulder-joints, 6 knee-joints, and 2 ankle-joints. All were associated with well-marked changes in the spine or hands.

In view of the almost universal involvement of the hands, we would suggest that an X-ray of the hands should be used as a screening test, particular attention being paid to the fourth and fifth metacarpals (fig. 7).

### Summary

A clinical and radiological study has been made of osteochondrodystrophy affecting three generations of a family. The condition has been transmitted as a mendelian recessive factor to both sexes.

X-ray study of the hands, vertebral column, and pelvis revealed all grades of changes in the 31 members affected. Changes in the fourth and fifth metacarpals were the commonest stigmata; and it is suggested that radiography of hands should be used as a screening test.

Part of this study was carried out at the Institute of Clinical Research of the Middlesex Hospital. We are much indebted to Dr. F. Campbell Golding for his interpretation of some of the X-ray plates and for his helpful advice.

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## CORONARY-ARTERY DISEASE AND OBESITY

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"Is coronary-artery disease more common in the obese?" Surprisingly the answer is still in doubt, perhaps because most papers on the subject have, in fact, been concerned with measuring not obesity but excess weight.

That excess weight and obesity are not synonymous was demonstrated by Welham and Behnke (1942). Body components other than fat were shown to be responsible in some cases for increased relative weight (defined as actual weight divided by a standard weight and multiplied by 100). Despite this important clarification, attention continued to be confined almost exclusively to the question of excess weight in relation to various diseases.

Unfortunately there is disagreement even on the question: "Is coronary-artery disease more common in the overweight?"

The evidence has been reviewed by Keys (1955), who, after criticising the deductions made from life-insurance statistics, is inclined to accept evidence, such as that of Yater et al. (1948), that there is no significant difference between the relative weights of men with coronary-artery disease, and men in good health.

In a notable effort to resolve the confusion Kurlander et al. (1956) measured the relative weight and body fat in a group of Negro outpatients, and examined the relation of each to heart-disease. They found a pronounced relation between excess weight and heart-disease, but no significant relation between body fat and heart-disease. Unfortunately the control group raises misgivings; they were patients attending hospital for treatment who were found on examination to be free from heart-disease; and the results were not subjected to statistical analysis.

TABLE I—MEAN WEIGHT, HEIGHT, AND AGE, IN PATIENTS AND CONTROLS

| — | Patients ($n=48$) | | Controls ($n=52$) | |
|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. |
| Weight (lb.) .. .. | 151·8 | 21·7 | 156·3 | 24·3 |
| Height (cm.) .. .. | 169·3 | 5·1 | 168·9 | 7·3 |
| Age (yr.)* .. .. | 57·3 | 9·1 | 52·8 | 10·5 |

* $t=2·4$. $P<0·02>0·01$.

In view of these facts, and because the subjects were Negroes, I decided to repeat the investigation, using an improved control group, and with expert statistical guidance in selection and analysis of measurements.

*Investigation*

A group of forty-eight white hospital patients, with recent onset of coronary-artery disease, who were all free from complications, and in whom the diagnosis had been confirmed by electrocardiogram, were matched with a control group of fifty-two healthy males, selected at random from the files of a National Health Service practice.

TABLE II—RELATIVE WEIGHT OF PATIENTS AND CONTROLS

| — | Patients | | Controls | |
|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. |
| Relative weight (%) .. | 106·8 | 14·5 | 111·2 | 16·9 |

TABLE III—FREQUENCY DISTRIBUTION OF RELATIVE WEIGHT

| Relative weight (%) .. | 70–79 | 80–89 | 90–99 | 100–109 | 110–119 | 120–129 | 130+ | Total |
|---|---|---|---|---|---|---|---|---|
| Patients | 2 | 3 | 8 | 13 | 15 | 4 | 3 | 48 |
| Controls | 0 | 5 | 11 | 9 | 11 | 9 | 7 | 52 |

$t=0·44$. $n=98$. $P=0·7$.

The groups were matched for sex (male), age (35–75), nationality (British), place of domicile (north-west London), and religion (Christian). The last three factors might have affected dietary habits. The patients and controls were then measured for weight, height, and skinfold thickness. The latter is an accepted measure of body fat (Keys and Brozek 1953, Brozek et al. 1954, Edwards et al. 1955, Pitts 1956). The Harpenden skinfold calliper was used (Edwards et al. 1955) according to the technique described by Brozek and Keys (1951). Skinfold measurements were taken at 6 sites.

Table I shows a fairly good match for weight, height, and age. The age difference was found to be possibly significant. The age factor is discussed further below.

*Relative Weight*

In transforming actual weight to relative weight the standard tables given by Kemsley (1952) for an English population were used. Tables II and III give the means and the frequency distribution respectively. The *t*-test applied to these results shows no significant difference.

TABLE IV—FREQUENCY DISTRIBUTION OF SKINFOLD THICKNESS

| Skinfold (mm.) .. | | <5 | 5–9 | 10–14 | 15–19 | 20–24 | 25–29 | 30–34 | Total |
|---|---|---|---|---|---|---|---|---|---|
| Mid-axillary | Patients | 0 | 10 | 14 | 14 | 8 | 2 | 0 | 48 |
| | Controls | 2 | 16 | 10 | 11 | 9 | 3 | 1 | 52 |
| Triceps | Patients | 1 | 22 | 18 | 6 | 1 | 0 | 0 | 48 |
| | Controls | 5 | 22 | 14 | 8 | 3 | 0 | 0 | 52 |
| Biceps | Patients | 22 | 23 | 1 | 2 | 0 | 0 | 0 | 48 |
| | Controls | 26 | 25 | 1 | 0 | 0 | 0 | 0 | 52 |
| Nipple | Patients | 1 | 8 | 5 | 12 | 13 | 8 | 1 | 48 |
| | Controls | 1 | 13 | 8 | 8 | 9 | 10 | 3 | 52 |
| Sub-scapular | Patients | 9 | 15 | 18 | 5 | 1 | 0 | 0 | 48 |
| | Controls | 0 | 13 | 17 | 12 | 8 | 2 | 0 | 52 |
| Supra-illiac | Patients | 3 | 12 | 16 | 12 | 5 | 0 | 0 | 48 |
| | Controls | 7 | 18 | 14 | 7 | 3 | 2 | 1 | 52 |

The first conclusion then, from the present findings, is that there is no evidence that the group with coronary-artery disease is overweight.

*Body Fat*

Table IV gives the frequency distribution of the skinfold measurements for each of the 6 sites. When transformed to a logarithmic scale (Edwards et al. 1955), they yielded the data in table V, which shows that the mean values were greater in the patients than in the controls at all sites. As it was theoretically possible for the difference to be related to one or all of the three factors weight, height, and age, scatter diagrams were constructed relating the skinfold measurements to each—a total of 18. Only the diagrams relating skinfold to weight suggested any correlation, and this was confirmed when the respective coefficients of regression were tested for significance (tables VI and VII). Figs. 1–3 reproduce the scatter diagrams for nipple skinfolds.

TABLE V—SKINFOLD THICKNESS OF PATIENTS AND CONTROLS (LOG. SCALE) AT 6 SITES

| Site of skinfold | Patients ($n=48$) | | Controls ($n=52$) | |
|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. |
| Midaxillary .. .. | 205·4 | 24·7 | 199·6 | 30·5 |
| Triceps .. .. .. | 190·4 | 19·5 | 184·4 | 26·1 |
| Biceps .. .. .. | 143·8 | 10·5 | 137·3 | 9·8 |
| Nipple .. .. .. | 213·9 | 26·5 | 207·5 | 31·1 |
| Subscapular .. .. | 206·1 | 17·3 | 204·6 | 20·5 |
| Suprailiac .. .. | 195·6 | 25·9 | 186·3 | 30·5 |

One can now proceed with the analysis of the measurements, in the knowledge that age and height can be ignored as factors affecting the relation between skinfold thickness and weight.

TABLE VI—SKINFOLD THICKNESS AT 3 SITES: SIGNIFICANCE TESTS FOR COEFFICIENTS OF REGRESSION ON AGE AND HEIGHT RESPECTIVELY

| — | | Patients ($n=48$) | | | | Controls ($n=52$) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | b | Sb | t | P | b | Sb | t | P |
| Mid-axillary | Age | 0·46 | 0·39 | 1·2 | 0·2 | 0·54 | 0·40 | 1·3 | 0·2 |
| | Height | −0·36 | 0·70 | 0·52 | 0·6 | −1·1 | 0·56 | 2·0 | 0·05 |
| Triceps | Age | −0·61 | 0·30 | 2·0 | 0·05 | −0·43 | 0·28 | 1·5 | 0·1 |
| | Height | 0·80 | 0·54 | 1·5 | 0·1 | −0·38 | 0·40 | 0·93 | 0·3 |
| Biceps .. | Age | −0·67 | 0·50 | 1·3 | 0·2 | 0·02 | 0·40 | 0·04 | 0·9 |
| | Height | 0·58 | 0·30 | 1·9 | 0·05 | 0·35 | 0·59 | 0·59 | 0·6 |

TABLE VII—SKINFOLD THICKNESS AT 6 SITES: SIGNIFICANCE TESTS FOR COEFFICIENTS OF REGRESSION ON WEIGHT (LOG. SCALE)

| Site of skinfold | Patients ($n=48$) | | | | Controls ($n=52$) | | | |
|---|---|---|---|---|---|---|---|---|
| | b | Sb | t | P | b | Sb | t | P |
| Midaxillary .. | 0·80 | 0·12 | 6·7 | <0·01 | 0·83 | 0·13 | 6·4 | <0·01 |
| Triceps .. | 0·51 | 0·10 | 5·1 | <0·01 | 0·60 | 0·13 | 4·6 | <0·01 |
| Biceps .. | 0·94 | 0·17 | 5·5 | <0·01 | 0·80 | 0·14 | 5·7 | <0·01 |
| Nipple .. | 0·96 | 0·10 | 9·6 | <0·01 | 0·87 | 0·13 | 6·7 | <0·01 |
| Subscapular .. | 0·54 | 0·09 | 6·0 | <0·01 | 0·38 | 0·10 | 3·8 | <0·01 |
| Suprailiac .. | 0·82 | 0·13 | 6·3 | <0·01 | 0·72 | 0·14 | 5·1 | <0·01 |

The regression lines for skinfold thickness of weight lie with that for the patients uppermost (fig. 4). In other words, at any given weight within the experimental range, skinfold thickness is greater in the patients than in the controls. There remains a statistical test for the validity of this result—namely, the technique of analysis of covariance (see Snedecor 1946).

The first step is a test for significance between regression coefficients in each of the 6 pairs of measurements. No significant difference was found. In other words, the regression lines are, for practical purposes, parallel (table VIII, $F_1$).

The second step is a test for significance for weight-adjusted means. The difference was found to be significant at P values between 0·01 and 0·02 (table VIII, $F_2$).

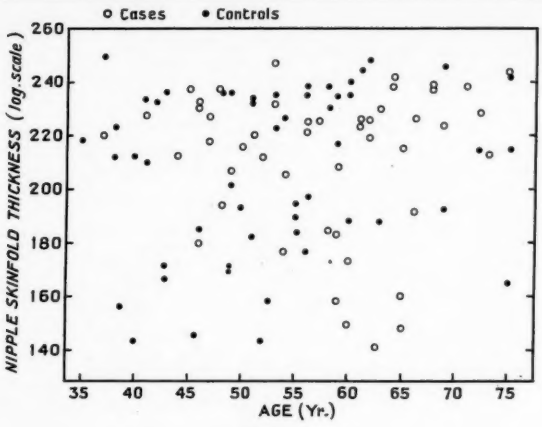


Fig. 1.

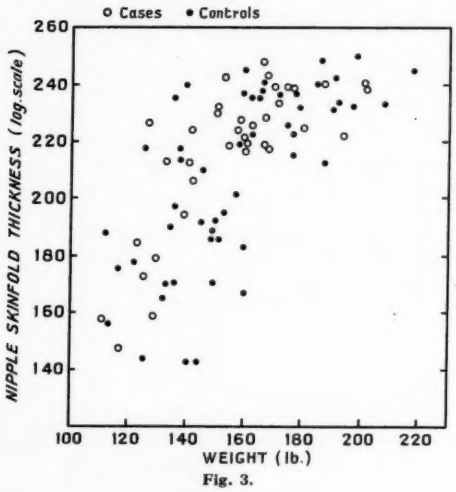


Fig. 3.

## Discussion

The present study showed that there was no significant difference between the relative weight of a group of patients with uncomplicated coronary-artery disease, and that of a group of healthy controls.

On the other hand, the patients were found to have a significantly increased mass of body fat. The corollary is that the patients had a smaller active-tissue mass, which obviously follows if total mass is the same in both groups. The first sketch in fig. 5 illustrates this. The second sketch makes a comparison with the findings of Kurlander et al. (1956), described above.

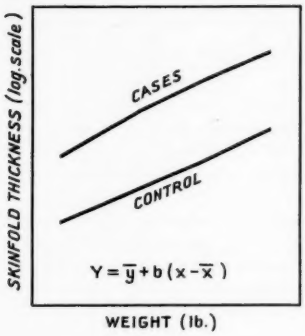


Fig. 4.

Although the question posed at the start has been answered, various supplementary questions arise, amongst them being why and how? But one can only speculate on these problems at present.

There might be poor muscle development,

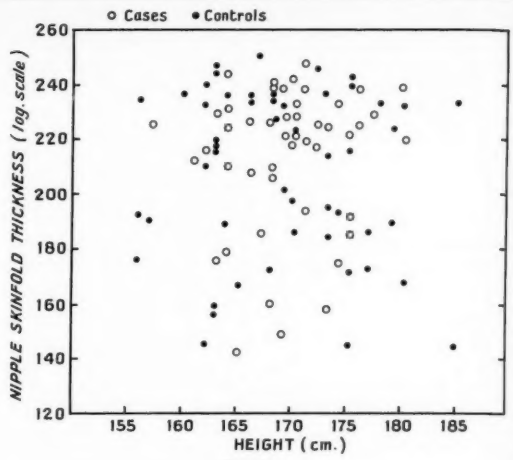


Fig. 2.

perhaps implied by a reduced active-tissue mass, in those engaged in light or sedentary work, and there is evidence that coronary-artery disease is more frequent in this group than in those whose work calls for physical effort (Morris et al. 1953). Perhaps lightly muscled people do not undertake heavy work or enjoy physical exercise, and thus fail to obtain the protection that both these activities seem to provide.

Alternatively the space previously occupied by muscles now partially atrophied might be filled by fatty tissue. Observations are rare on body composition in different

TABLE VIII—ANALYSIS OF COVARIANCE-SIGNIFICANCE TESTS BETWEEN REGRESSION COEFFICIENTS AND BETWEEN WEIGHT-ADJUSTED MEANS

| Site of skinfold | $F_1$* | P | $F_2$† | P |
|---|---|---|---|---|
| Midaxillary .. .. | 0·05 | >0·1 | 5·3 | >0·01 |
| Triceps .. .. .. | 0·27 | >0·1 | 5·5 | >0·01 |
| Biceps .. .. .. | 0·39 | >0·1 | 4·7 | >0·01 |
| Nipple .. .. .. | 0·28 | >0·1 | 7·4 | <0·01 |
| Subscapular .. .. | 1·28 | >0·1 | 4·9 | >0·01 |
| Suprailiac .. .. | 0·36 | >0·1 | 8·4 | <0·01 |

* $n = 96$. † $n = 97$.

nationalities, but in view of the difficulty of relating the variable incidence of coronary-artery disease in different countries to dietary differences (Yudkin 1957), they would be of great interest. Dr. S. E. Finlay (personal communication 1958), for example, states that Indian students at Leeds University tend to be fatter, and to have a smaller active-tissue mass, than their English contemporaries.

My findings suggest that clinicians, who have been

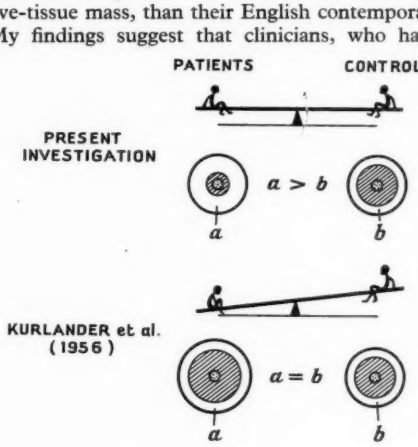


Fig. 5.

impressed by the fact that patients with coronary-artery disease seem to be " fat " (Levine and Brown 1929), may have been looking at the other face of the same coin seen by research-workers who have found no difference in weight in these patients compared with healthy men.


### Summary

Forty-eight patients with coronary-artery disease have been compared with fifty-two healthy controls in respect of relative weight and body fat as measured by skinfold calliper.

No significant difference was found in the relative weight of the two groups, but the patients had a significant increase in body fat as compared to the controls.


I should like to acknowledge the advice and encouragement received from Dr. Keith Ball and Dr. Horace Joules, of the Central Middlesex Hospital, London, who also granted access to their hospital patients; from Dr. J. M. Tanner, of the Child Study Centre, University of London; from Mr. J. A. Heady, of the Medical Research Council Social Medicine Research Unit, London Hospital, particularly for statistical guidance; and from Dr. S. E. Finlay, of the Department of Student Health, University of Leeds.

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## EFFECT OF CHOLESTEROL, CHOLESTEROL ESTERS, AND NEUTRAL FATS ON FIBRINOLYSIS


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Greig (1956) found that the plasma had less fibrinolytic activity after a fatty meal than after a non-fatty meal, and he showed that the addition of cream to plasma inhibited fibrinolysis. Greig and Runde (1957) found that if the fatty meal consisted of vegetable oils, such as coconut oil or sunflower-seed oil, fibrinolysis was not inhibited, and might be enhanced; butter fat, on the other hand, reduced the fibrinolytic activity. Kwaan and McFadzean (1957) showed that clots in the ear veins of rabbits lysed slowly when the animals were given a high-cholesterol diet. There is evidence therefore to suggest that lipids inhibit fibrinolysis, and we report here a series of experiments on the in-vitro effect of cholesterol, cholesterol esters, and neutral fats on this process.

### Methods

*Collection of Plasma Samples*

Venous blood was drawn from healthy subjects into dry all-glass syringes, through stainless-steel needles, and was then mixed with 1/9 of its own volume of freshly prepared 3·8% sodium citrate. The sample was spun immediately at 4°C and 2500 r.p.m. for 10 minutes, and the plasma was sucked off into dry tubes. All subsequent manipulations were done in a refrigerated room (4°C) using glassware and reagents that had been in the room overnight.

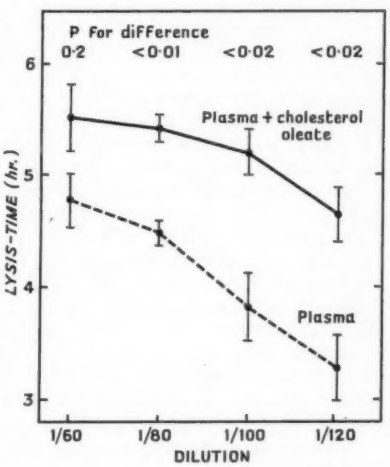
*Addition of Test Substances*

*Cholesterol and its esters.*—Suspensions of cholesterol and of its stearate, oleate, and acetate were prepared by dissolving about 1 g. of each substance in 20 ml. of warm acetone, pouring the solution quickly into 100 ml. of distilled water, stirring steadily throughout, and filtering the suspension through glass wool. The acetone was boiled off, and the cholesterol content of the suspension was measured by Anderson and Keys' (1956) modification of the method of Abell et al. (1952). Each suspension was then diluted so that, on hydrolysis, the free cholesterol content was 125 mg. per 100 ml.

Plasma was diluted 1/60 with (a) buffered saline, or (b) buffered saline containing 1/60 of the various cholesterol suspensions. From these 1/60 dilutions, plasma dilutions of 1/80, 1/100, and 1/120 were prepared by the addition of buffered saline. If the added cholesterol had been derived from the plasma, it would have represented a rise in cholesterol content of 125 mg. per 100 ml.

Buffered saline solution was made by taking 50 ml. of a solution containing 9·71 g. hydrated sodium acetate and 14·71 g. sodium barbitone in 500 ml. water, adding 45 ml. of 0·1 *N* hydrochloric acid, making up to 1 litre with 0·85% sodium-chloride solution, and adjusting the pH to 7·4 with 0·1 *N* hydrochloric acid.

*Neutral fat.*—10% oil-in-water emulsions of lard, butter fat, corn oil, olive oil, and coconut oil were prepared. The fats were washed three times with 1% sodium bicarbonate and once with water, to remove free fatty acids, the washings being performed at temperatures just above the melting-point of the fats. The washed fats were then passed through a hand homogeniser with the emulsifying solution ('Tween 60' 0·5% and glucose 5%, in water). Plasma was diluted 1/60 with (a) buffered saline, (b) buffered saline to which neutral fat emulsion had been added, or (c) buffered saline containing an equivalent volume of the tween-glucose emulsifying solution, to find out if the vehicle for the fat was affecting lysis. From these 1/60 dilutions, 1/80, 1/100, and 1/120 plasma dilutions were prepared by the addition of buffered saline.




**Mean lysis-times ($n = 12$) for diluted plasma alone and diluted plasma to which a suspension of cholesterol oleate had been added.** The vertical lines show the standard errors of the mean values.

By adding different volumes of neutral-fat emulsion we could produce various plasma-triglyceride levels, and in this way we tested the effect of amounts of neutral fat, which, had they been derived from the plasma, would have represented plasma-triglyceride concentrations of 200, 400, 1000, and 2000 mg. per 100 ml.

*Clotting and Estimation of Lysis-time*

4 ml. of diluted plasma was pipetted into a test-tube, and 0·2 ml. of human thrombin solution containing 20 units per ml. (Lister Institute) was added from a microburette. The time interval between venepuncture and clotting was always between 25 and 30 minutes. The tubes were then incubated at 37°C, and were inspected every half-hour; the time taken for complete lysis of the clot was recorded for each dilution of plasma, and for the plasma to which the test materials had been added.

### Results

*Cholesterol and its esters.*—Twelve tests were done and the mean lysis-times for the various systems were compared. Cholesterol itself, and cholesterol acetate and stearate, delayed lysis slightly, but the difference between these systems and plasma alone was not significant. Cholesterol oleate, however, produced considerable inhibition (see figure).

*Neutral fat.*—Eight tests were done and in the concentrations used none of the fats changed the lysis-time.

### Discussion

There is no clear evidence that fibrinolysis plays any part in the normal working of the body. Hence it is unwise to try to apply our findings to any situation other than the artificial system from which they were derived.

As the only tested substance with any definite effect is cholesterol oleate, it is of interest that 86% of human cholesterol ester is in the form of oleate and linoleate (Lipsky et al. 1957). Changes in the total plasma-cholesterol level would therefore be accompanied by a changing cholesterol-oleate concentration. Greig and Runde (1957) noticed that fibrinolytic activity bore an inverse relation to the height of the serum-cholesterol level. Our findings may be relevant to this observation and to the work of Kwaan and McFadzean (1957) on the inhibitory effect of cholesterol feeding on fibrinolysis in the veins of the rabbit's ear, for, in the rabbit, dietary cholesterol is directly related to serum-cholesterol levels (Anitschkow 1933). We cannot, however, relate our findings to the work of Greig (1956) and Greig and Runde (1957) on the inhibition produced by fat feeding; for it has been shown that the serum-cholesterol in man does not vary significantly during an ordinary day's activity, and that it is not materially changed by a single fatty meal (Boyd 1935, Turner and Steiner 1939, Keys et al. 1956). Therefore one cannot readily account for the inhibitory effect of fat feeding in man by changes in the serum-cholesterol level, nor, in view of our results, in terms of changes in the neutral-fat content of the plasma. If one accepts that fat feeding does inhibit fibrinolysis, then changes in other blood-lipids must be responsible.

We are now examining the effect of phospholipids and free fatty acids. Our results so far show that added phospholipids have no effect on fibrinolysis, and that free fatty acids behave similarly when used in physiological concentrations (0·2–2·0 mEq. per litre). At much higher concentrations (20 mEq. per litre and over), although stearic acid is still without effect, linoleic and oleic acids seem to inhibit both clot retraction and lysis.

### Summary

The effect of suspensions of cholesterol and cholesterol esters, and of emulsions of neutral fats, on in-vitro fibrinolysis was assessed.

Cholesterol-oleate suspensions inhibited fibrinolysis significantly. The other substances did not.

We are grateful to Sir George Pickering for advice and encouragement.

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# STRIÆ GRAVIDARUM

## THEIR RELATION TO ADRENAL CORTICAL HYPERFUNCTION

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THE literature of the past century on the subject of striæ gravidarum reveals our lack of knowledge. Clinicians of the 19th century thought striæ were due to stretching of the skin, but closer attention to detail leads their successors to cast doubt upon this ætiology (Wilks 1861).

Early in this century many debilitating conditions—e.g., tuberculosis, typhoid fever, rheumatic fever, and longstanding suppurative states—were found to be associated with striæ. Thus contemporary thought linked their ætiology with malnutrition, protein loss, general debility, and toxic states, but the connection between these striæ and those of pregnancy was not understood (Parkes Weber 1905, Moore 1908, Rolleston 1908, Evans 1915).

The conception of " stretch marks " was soon to be upset further when adolescents of both sexes were seen with striæ, which were not necessarily associated with obesity (Sibley 1923, Sisson 1954), and thus more confusion was added. Interest was most intense amongst the general physicians of the early half of this century, and there were few contributing thoughts from obstetricians, who seemed content to accept the comfortable theory of skin stretch. This is still accepted by most authors of present-day obstetric textbooks. But Browne and Browne (1955), Greenhill (1955), Holland and Bourne (1955), Eastman (1956) and Jeffcoate (1957), form a minority group by suggesting a relation with adrenal cortical hyperactivity.

After Selye's stress theory (1946), and when adrenal cortical hormones were used therapeutically, the possible link between striæ noted as side-effects, and adrenal cortical function became apparent for the first time. Concurrently much evidence of adrenal cortical hyperactivity during normal pregnancy was presented, with the natural suggestion of a relation between striæ and the adrenal cortex (Venning 1946, Robinson et al. 1955, Jailer 1956, Gold 1957, Migeon et al. 1957), though this was not generally appreciated.

Thus further studies in accordance with this more modern concept of the ætiology of striæ gravidarum seemed opportune.

### Investigation

#### RELATION BETWEEN SKIN STRETCH AND STRIÆ

If doubt were to be cast upon skin stretch as the cause of striæ obviously evidence had to be produced in support.

116 primigravidæ were followed throughout pregnancy from the 14th week or earlier, by making detailed measurements of girth at the level of the umbilicus and of the upper border of the symphysis pubis. In pregnancy the greatest increase in abdominal girth is at the level of the umbilicus, and women's hips are widest at the level of the symphysis pubis. The greatest skin stretching should occur at the levels of the greatest girth increases. The breasts, a common site for striæ gravidarum, were not included in this part of the study because of the unreliability of their measurements found previously. The measurements were standardised in that the same firm type of consultation couch was always used, and I personally made each reading at every visit.

At the end of this study the degree of stretch (%) was related to the time of onset of striæ on the abdominal wall and the hips.

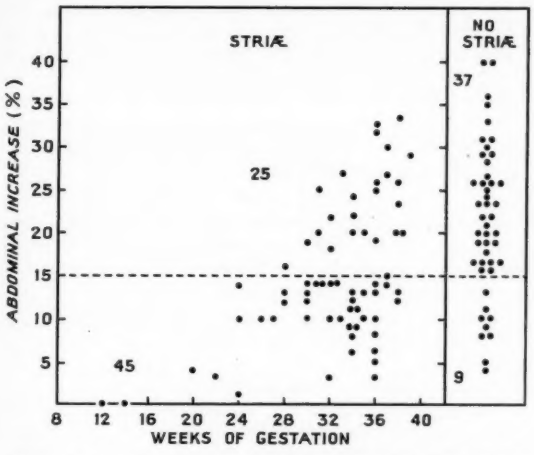


**Fig. 1—The relation between increased abdominal girth and the time of development of striæ. Those not developing striæ are simply related to the girth increase.**

*Increase in Abdominal Girth Related to Striæ Formation*

Fig. 1 shows that:

70 women developed striæ, and 46 did not.

45 of the 70 developed their striæ with less than 15% of stretch, and the other 25 stretched 15% or more before striæ appeared.

37 of the 46 who did not develop striæ stretched more than 15%.

Of 62 women who stretched 15% or more, 25 (40%) developed striæ while 37 did not; and of 54 women who stretched less than 15%, 45 (83%) developed striæ while 9 did not.

Of 12 women who stretched 30% or more, only 4 (33%) developed striæ.

Thus those women who were destined to develop abdominal-wall striæ usually did so at the lower levels of stretch. The 15% level is purely arbitrary, and was selected because it is about midway between the average range of stretch. Most women who did not develop striæ resisted the greatest degrees of stretch.

When several levels of stretch are examined it is found that:

Of those who stretched less than 15%, 83% developed striæ.
Of those who stretched 15–29%, 42% developed striæ.
Of those who stretched 30% or more, 33% developed striæ.

These findings are not consistent with the theory that stretching is the prime cause of striæ. If this were so stretching, as it increased, would produce striæ in all women. This was not found. The fact that there was a group of non-striated women is conclusive proof of the presence of some factor in the production of striæ other than stretch alone; for at any level of stretch selected for examination it can be seen that some women did and some did not develop striæ.

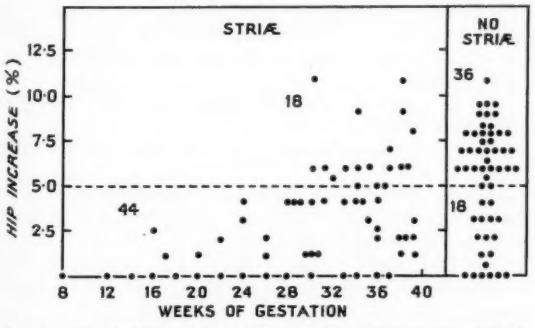


**Fig. 2—The relation between increased hip measurement and the time of development of striæ. Those not developing striæ are simply related to the increased hip measurement.**

If this other factor were chance, then, whether we were dealing with groups above or below 15% of stretch, we should expect a fairly even division between the striated and non-striated women. But this was not found. In fact the reverse tendency was shown.

Since abdominal-wall striæ are neither fully dependent upon stretch nor upon chance, the only reasonable explanation is that each woman has her own individual "striæ factor". Some women develop their striæ before any increase in girth takes place. Some require more stretch and reach more advanced pregnancy before striæ appear, whilst others are able to resist the greatest stretching without developing striæ.

*Increase in Hips Related to Striæ Formation*

Although smaller degrees of stretch were involved than in the abdominal group, these results were similar (fig. 2), showing that most women destined to develop hip striæ did so at the lower levels of stretch. 15 primigravidæ developed fresh hip striæ before there was any increase in measurement, while 16 others developed striæ within the 2·5% range of stretch. Thus 31 out of 62 women developed striæ with 2·5% or less of stretch.

*Conclusion*

No direct relationship could be demonstrated between the degree of skin stretch and the production of striæ gravidarum. Striæ have developed with widely varying degrees of stretch in different individuals.

## SEARCH FOR THE "STRIÆ FACTOR"

Concurrently a relationship was sought between a blood-glucose "lag" and striæ gravidarum.

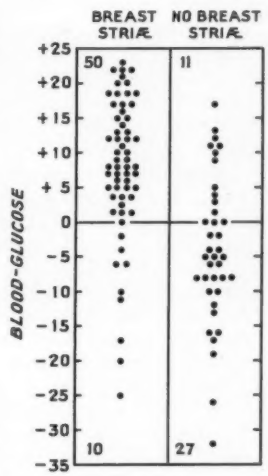


**Fig. 3—The relation between blood-glucose variations and the development or not of breast striæ.**

A full glucose-tolerance test was conducted on 98 of the same women between the 34th and 36th weeks of pregnancy. One highly trained biochemist conducted all these tests under standard laboratory conditions. A modified Haslewood and Strookman method was used for the blood-glucose estimations. Blood-glucose was examined rather than the more usual blood-reducing substances of routine work because it was considered a truer indication of adrenal cortical activity.

Much work has been published regarding this delay in return of blood-glucose to fasting levels at the 2-hour period in pregnancy, and it is accepted as evidence of increased adrenal cortical function during pregnancy (Albright 1943, Conn et al. 1948, Forsham et al. 1948, Appel et al. 1953, Burns et al. 1953, Persky et al. 1955). Because this lag was seen in many normal pregnancies, I decided to test its relation to striæ gravidarum (fig. 3).

The plus and minus figures for blood-glucose refer to the amount of lag or otherwise (in mg. per 100 ml.) at the 2-hour

level. Thus, if at 2 hours the blood-glucose has failed to return to the fasting level by 17 mg. per 100 ml., this figure was recorded as +17. The blood-glucose findings were related to breast, abdominal, and hip striæ, but breast striæ were thought to be more reliable because of the relative elimination of the stretch factor.

The results clearly show that women who developed breast striæ had a degree of blood-glucose lag far more often than not (50 out of 60), whereas the control group, who did not develop breast striæ, showed the opposite tendency (11 out of 38).

It may be argued that as most women show a glucose lag in pregnancy, and as more women than not show breast striæ, then most cases would be expected to fall within the left upper quadrant of fig. 3. But this is shown to be false when the non-striated group is examined; for those who do not get striæ tend not to have a glucose lag. Also if looked at horizontally it would be seen that of 61 women with glucose lags 50 had striæ, whereas of 37 without glucose lags only 10 had striæ.

Statistically the hypothesis of no relation between the development of breast striæ and variations in the blood-glucose is rejected at the 1% level of significance, using a $\chi^2$ test.

With the abdomen and hips there was again strong statistical evidence of a relation between striæ gravidarum and blood-glucose lags.

*Conclusion*

Increased blood-levels of ketogenic steroids cause a lowering of glucose tolerance, and these steroids are known to be increased in pregnancy. Because close relation was shown between striæ and lowered glucose tolerance, it is tempting to suggest that the production of striæ is closely related to these increased steroid levels.

## RELATION BETWEEN ACNE AND STRIÆ GRAVIDARUM

Acne is a well-accepted sign of the circulation of excess ketogenic steroids. In pregnancy and during menstruation facial acne is extremely common, particularly in minor degrees, on the forehead or round about the mouth and chin. Women rarely complain of it, being content to rely on cosmetic management. But when this sign is expressly sought, as in this study, and recorded at each visit it is found far more frequently. More interesting than its finding, however, is its very close time relation to breast striæ. In order to test this relation a graph relating the onset of breast striæ with the onset of acne was produced (fig. 4). There is a very striking linear relation.

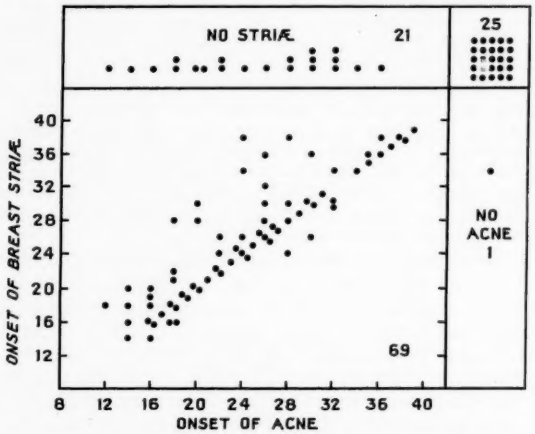


**Fig. 4—The time relation between the development of breast striæ and the onset of facial acne.**

90 women of the 116 studied showed facial acne at some stage of pregnancy, and 69 of these 90 developed both acne and breast striæ. In most these two signs appeared within a 3-week period, whilst half developed them simultaneously.

It is difficult to avoid the suggestion that the influence causing the one causes the other. The relation between the onset of hip striæ and the onset of acne, although not quite so close, was nevertheless definite.

## FURTHER RELATIONSHIPS

Many other cross relations from this detailed clinical study have been revealed by the use of a specially designed punch card. Some of these are worth reporting briefly:

*Previous Acne and Striæ Gravidarum*

Those women who admitted previous acne showed a greater tendency to develop striæ during pregnancy (68% as compared with 54%).

*Previous Acne and Acne in Pregnancy*

Those who had previously had acne not only developed it more frequently during pregnancy (85% compared with 62%), but they also developed it much earlier.

*Previous Acne and Previous Obesity*

There was a higher tendency in favour of this relation, namely 32% as against 24%.

*Excessive Weight Gain in Pregnancy and Striæ Gravidarum*

26 lb. and over was considered as excessive weight gain in pregnancy. Women who became unduly heavy had a greater tendency to striæ formation whether on the breasts, abdomen, or hips. This has already been proved not to result from the stretching effect of excessive weight. It rather suggests a type tendency.

*Toxæmia of Pregnancy and Striæ Gravidarum*

Only those women whose toxæmia necessitated admission to hospital were classified for this purpose. There was a decided tendency for women with toxæmia to have a higher incidence of striæ on the breasts, abdomen, or hips (87% in the toxæmia group as against 53% in the non-toxæmia group). This could be interpreted as suggesting a relation between toxæmia of pregnancy and adrenal cortical hyperactivity. There is much clinical and laboratory evidence in favour of this suggestion, but there is also much conflicting evidence, and in the present state of our steroid knowledge its true significance must remain in doubt.

*Complexion and Striæ Gravidarum*

70% of those with medium and fair complexions developed breast striæ, whereas only 41% of those who were dark did so.

Individually the above relationships do not provide proof of a connection between striæ gravidarum and adrenal cortical hyperfunction, yet collectively they support the general theme.

*Striæ Gravidarum and Application of Olive Oil*

As the rubbing in of olive oil is regarded universally as a prophylactic of striæ, it seemed worth collecting some factual evidence. Each of the 116 primigravidæ was left to make her own decision as to whether she would rub in olive oil or not after the current views had been explained to her. 50 women used it while 66 did not. The results show that:

Of 50 who used olive oil nightly, 36 (68%) developed abdominal striæ.

Of 66 who did not use oil, 36 (55%) developed abdominal striæ.

Thus not only did the nightly rubbing in of olive oil fail as a prophylactic, but it actually appeared to predispose to the development of striæ. If olive oil had no influence either way then the chance finding should be about 50% in each group, for the numbers are large enough to expect this.

The conclusion may be drawn that either the olive oil itself or the massage predisposed to striæ formation.

*The Role of Stretch*

I do not intend to suggest that stretch plays no part in the production of striæ gravidarum. It does. The best evidence for this is the unilateral appearance of striæ around previous gridiron abdominal incisions. Primigravidæ who have such scars, and who are destined to develop striæ, always get their earliest striæ near the scar, although it may be 2 or more weeks before symmetrical striæ appear. This observation suggests strongly that the distorted skin tensions around the scar play their part in the formation of striæ (figs. 5 and 6). Many women, not destined to develop striæ, go to term without striæ despite their scars.

**Fig. 5—Early striæ gravidarum appearing at each end of an appendicectomy scar (primigravid pregnancy of 30 weeks).**

**Fig. 6—Striæ gravidarum alongside an appendicectomy scar in a primigravid pregnancy of 34 weeks. Note absence of striæ on the left. At 38 weeks, in this case, there were extensive bilateral striæ.**

It seems reasonable to suggest, therefore, that skin stretch and the " striæ factor " are both required for the production of striæ, and without the latter no degree of stretch will produce striæ.

## Summary

Striæ gravidarum should no longer be considered as " stretch marks ". There is strong evidence that they are closely related to adrenal cortical hyperactivity.

In a study of 116 primigravid pregnancies it was shown that:

The formation of striæ gravidarum does not depend directly upon skin stretching; this only influences the production of striæ in the presence of a " striæ factor ".

There is a close relation between lowered glucose tolerance in late pregnancy and the development of striæ gravidarum.

There is a close relation between acne, a sign of adrenal cortical hyperactivity, and breast striæ, particularly as regards time of onset.

Several other clinical findings all lend support to an association between striæ gravidarum and adrenal cortical hyperactivity.

Olive-oil massage does not prevent striæ gravidarum.

The substance of this paper was included in a thesis accepted by the University of Adelaide for the degree of M.D.

I am grateful to Sandoz Ltd., Australia, for defraying the total expenses of this study.

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# VARUS DEFORMITY OF THE ELBOW FOLLOWING SUPRACONDYLAR FRACTURES OF THE HUMERUS IN CHILDREN

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A GUNSTOCK or varus elbow is the commonest late deformity in supracondylar fractures of the humerus (fig. 1). It is usually caused by failure to correct the rotational displacement of the distal fragment. Madsen (1955) has again emphasised the need for exact reduction in the treatment of these fractures, and has reiterated the views of Windfeld (1948) and others of the importance of rotational displacement as a cause of late deformity. That internal rotation is part of the established deformity is shown by the fact that a gunstock elbow is almost always accompanied by an apparent increase in internal rotation of the shoulder when the flexed elbow is used as a lever. As Madsen says, internal rotation is the most difficult displacement to reduce and to hold reduced.

### Correction of the Fracture

Internal rotation of the distal fragment may be recognised radiologically when it is not apparent on clinical examination. The anteroposterior radiograph very frequently shows that the supracondylar ridges on the upper fragment are of unequal length, the internal ridge commonly being longer than the external (figs. 2 and 3). The lateral radiograph then shows that the longer spike of the upper fragment is pointed forwards (figs. 2 and 3). Provided that the lateral radiograph is correctly centred on the elbow-joint, the forward direction of the spike of the medial supracondylar ridge indicates that the shaft of the humerus is externally rotated, and this results in a relative internal rotation of the lower fragment.

**Fig. 1.**

Fig. 3 illustrates how the persistence of internal rotation gives rise to the gunstock deformity; the lateral part of the lower fragment becomes hitched and reduced,

DR POIDEVIN: REFERENCES—*continued*

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Fig. 2.

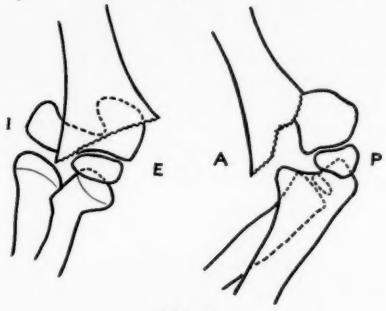


Fig. 3.

while the medial end remains behind the long spike of the medial supracondylar ridge. This rotational displacement further accentuates the varus deformity, for the inner border of the humerus is now shorter than the outer.

Manipulative correction may be modified on the basis of this observation.

The fracture should be reduced under radiographic control; once it has been found that the fracture requires reduction the child may be spared the discomfort of much radiography until anæsthetised. Traction is applied with the elbow flexed and the forearm pronated, countertraction being supplied by an assistant holding the upper arm and attempting to keep the humerus in neutral rotation. Lateral shift of the distal fragment is first corrected, and then rotation of the lower fragment, using the forearm as a lever. Posterior angulation is then abolished by pressure of a thumb on the olecranon and increasing the flexion of the elbow. Fig. 4 shows how it is possible to overcorrect the angulation; the longer spike of the medial supracondylar ridge is now pointing backwards, indicating that the lower fragment is externally rotated, for the radiograph is still correctly centred on the elbow joint. Fig. 5 shows the same elbow after correction of the external rotation.

Fig. 4.

The internal rotation may be caused immediately by the nature of the fall, and perpetuated by the position in which the arm is held after the injury—i.e., across the abdomen supported by the other hand. Moreover this position may predispose to redisplacement after reduction, and the corrected deformity would therefore seem to be more easily maintained at extreme flexion. Sir Robert Jones' principle was to put up the elbow " at five minutes past the hour ", or as much flexed as was consistent with an easily palpable pulse. One disadvantage of this is the delay in attaining full extension of the elbow, so that the varus deformity may not be appreciated for six months or a year. The presence of varus may be suspected, however, if radiography shows that the internal rotation has not been corrected or maintained.

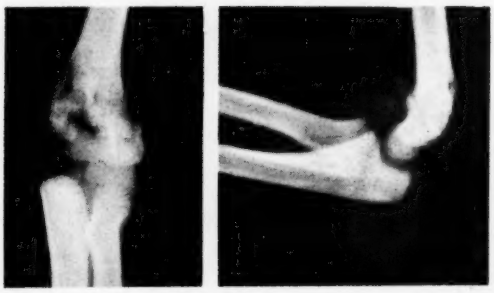

Fig. 5.

Fig. 6.

### Late Correction of the Deformity

Once fully developed the gunstock deformity does not improve. Although, as Attenborough (1953) points out, considerable remodelling of the lower end of the humerus takes place, this affects the anteroposterior displacements and angulations without altering the varus angulation or the internal rotation. The deformity is very unsightly, and, although joint function may not be greatly impaired, the child's parents usually request an operation, if mainly for cosmetic reasons.

Fig. 7.

The correction is done by means of a wedge osteotomy,

Fig. 8.

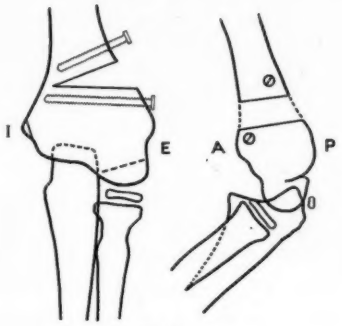


Fig. 9.

the triangular wedge having its base on the lateral supracondylar ridge. In the past the operation has been not without hazard, and the osteotomy has been found difficult to control. The following procedure gives a good exposure, robs the operation of some of its dangers, provides a method for satisfactory control of the osteotomy, and allows of earlier mobilisation of the elbow:

The lower end of the humerus is approached from the back through an incision splitting the triceps. The lateral half of the triceps is detached from its insertion and reflected upward. By this means, the posterior surface and lateral border of the humerus can be seen. The ulnar nerve can also be displayed on the medial side. Two drills are inserted which can act as guide to the plane of the desired osteotomy and their position is checked by radiography (figs. 6–8). Before the bone is cut across, two screws are inserted above and below the guides and parallel to them.

The wedge is then excised: the bone is cut across with a mechanical saw as far as possible, but the inner periosteum is left intact as a hinge. The cut surfaces are then approximated by tightening a wire connecting the heads of the two screws (figs. 8 and 9). This may be done most easily by threading the wire through a small hole in the neck of one of the screws before full insertion, and round the neck of the other screw. Further insertion of the first screw will then tighten the wire. The rotational deformity is corrected at the same time by placing the screws in different positions in the coronal plane (figs. 8 and 9).

### Summary

Cubitus varus following supracondylar fractures of the humerus in children is usually caused by internal rotation of the distal fragment.

This displacement may be recognised radiologically and can be treated by manipulative reduction under radiological control.

The established gunstock deformity may be corrected by a wedge osteotomy with internal fixation by screws.

My thanks are due to Mr. B. H. Burns and Mr. R. H. Young for permission to use their cases and for their help and encouragement. I am also grateful to the photographic department of St. George's Hospital for the clinical photographs and reproductions of the radiographs.

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## ATROPINE IN MONGOLISM

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McKusick (1957), writing on genetically determined drug idiosyncrasy, posed the question: "What is the basis for the not infrequently fatal idiosyncrasy of mongoloid idiots to agents of the atropine group?" Professor McKusick tells us that this knowledge of the sensitivity of mongol children to atropine is a "local pearl" at the Johns Hopkins Hospital, and that he has been unable to find a published reference to it. We have from time to time used atropine as preoperative medication in mongolism, and we have found no ill effects. Nevertheless, in view of its potential importance, we investigated the reaction of mongol children to atropine.

### Method

Two trials were made; in each there was a group of ten mongols and of ten mentally defective controls, matched for age, mental level, mobility, and general health. Cripples and children with obvious motor lesions were excluded. All the children were inpatients at the Fountain Hospital. Different patients were used in the two trials.

One drop of atropine 1% was instilled into the right eye of each child. The eyes were examined in natural daylight 15 minutes later, and then daily until the pupils became equal in size. Any difference in dilatation of the pupils was scored on a three-point scale, +++ representing a maximal difference.

Permission for the trial was sought from the mothers of the controls. It was pointed out that the drop of atropine

TABLE I—DEGREE OF DILATATION OF THE PUPIL 15 MINUTES AFTER INSTALLATION OF ATROPINE

| Trial 1 | | Trial 2 | |
|---|---|---|---|
| Mongols | Controls | Mongols | Controls |
| +++ | +++ | +++ | ++ |
| +++ | ++ | +++ | +++ |
| ++ | ++ | +++ | 0 |
| +++ | ++ | ++ | +++ |
| ++ | + | +++ | + |
| +++ | ++ | +++ | ++ |
| 0* | ++ | +++ | +++ |
| +++ | +++ | ++ | ++ |
| +++ | ++ | ++ | +++ |
| +++ | + | +++ | ++ |

Age range of mongols: 5–13 years. Mean = 9·1 years
" " controls: 4–13 years. Mean = 8·5 years
I.Q. range of mongols: 10–39 Mean = 25·6
I.Q. " controls: 3–65 Mean = 25·6

+++ = maximal dilatation of pupil
++ = moderate " " "
+ = slight " " "
0 = both pupils equal in size

* No dilatation occurred, and it was thought that the drop had missed the eye. This patient was not therefore included in the assessment of the results.

TABLE II—MONGOLS AND CONTROLS WITH AND WITHOUT FULLY DILATED PUPIL AFTER 15 MINUTES

| Score | Mongols | Controls | Total |
|---|---|---|---|
| ≧+++ | 14 | 6 | 20 |
| <+++ | 5 | 14 | 19 |
| Total | 19 | 20 | 39 |

$\chi^2=5{\cdot}797$. $P<0{\cdot}02$.

was quite harmless, and that atropine drops are often used by ophthalmologists in routine eye examinations.

## Results

The effect of the atropine drops was assessed in two respects: speed of dilatation as judged at the end of a 15-minute interval, and duration of dilatation as noted during daily observations.

*Speed of Dilatation*

The relative speed of dilatation is shown in table I.

An analysis of the results for the speed of dilatation is shown in table II, the case which did not respond being omitted. The mongols appeared to respond more rapidly to atropine than the controls ($\chi^2=5{\cdot}797$, $P<0{\cdot}02$).

TABLE III—SCORES FOR DURATION OF DILATATION OF PUPIL

| Trial 1 | | Trial 2 | | |
|---|---|---|---|---|
| Mongols | Controls | Mongols | Controls | |
| 39 | 15 | 24 | 13 | |
| 24 | 6 | 25 | 30 | |
| 44 | 17 | 38 | 20 | |
| 27 | 12 | 25 | 36 | |
| 37 | 16 | 31 | 38 | |
| 31 | 14 | 49 | 22 | |
| 23 | 24 | 37 | 33 | |
| 21 | 24 | 40 | 17 | |
| 26 | 29 | 35 | 29 | |
| .. | 26 | 30 | 44 | |
| 272 | 183 | 334 | 282 | Total |
| 30·2 | 18·3 | 33·4 | 28·2 | Mean |

There appears to be a slight, though not statistically significant, relation between age and speed of reaction for the whole group. If the eleven patients aged less than 7 years are excluded, then the significance of the difference between the groups rises ($\chi^2=7{\cdot}146$, $P<0{\cdot}01$).

*Duration of Dilatation*

The atropinised eye remained dilated for periods varying from 8 to 24 days. A score was registered for each patient by adding up the total number of + marks recorded; these are shown in table III.

These data have been analysed (table IV) in terms of scores of 25 and over, and 24 and under, this being the best point of division to show significance.

If the results of both trials are added, they are significant at the 1/20 level, though the second trial is not in itself significant.

## Discussion

This investigation, though preliminary and indicating the need for further work, tends to confirm McKusick's observation that mongols are hypersensitive to atropine. The speed of pupillary dilatation shows a difference significant at the 1/50 or 1/100 level, whilst the duration of dilatation gives a difference, the chance probability of which is 1/20.

TABLE IV—ANALYSIS OF SCORES FOR DURATION OF DILATATION

| Score | 25 or more | 24 or less | Total |
|---|---|---|---|
| Mongols .. | 15 | 4 | 19 |
| Controls .. | 8 | 12 | 20 |
| Total .. .. | 23 | 16 | 39 |

$\chi^2=4{\cdot}61$. $P<0{\cdot}05$.

The results of these trials do not show a clear differentiation between the mongol and control groups. There is, in fact, considerable overlap, which accords with other observations on different aspects of mongolism by Simon et al. (1954), and by Stern and Lewis (1957a and b, 1958). These workers found that, whilst there is a significant difference between mongols and controls in various aspects of their blood chemistry, there is also considerable overlap between the two groups, so that differences tend to be quantitative rather than qualitative.

For many years we have been intrigued to know whether the nervous system in mongolism would function more efficiently after suitable treatment in early postnatal life to correct assumed metabolic anomalies. Many of the anatomical abnormalities are determined in early intrauterine life, but Crome (1954) has shown that the weight of the mongol's brain is greater than that of most other mental defectives with a similar degree of retardation, and that it is relatively free from gross lesions.

The possible relation between the low muscle tone, which is a constant feature of mongolism, and atropine sensitivity raises interesting speculation. Since atropine inhibits acetylcholine, which is concerned with normal stimulation of skeletal muscle, the two phenomena may be related to the same basic metabolic defect in mongolism. If atropine sensitivity can be confirmed by other workers, it may guide the development of rational therapy.

## Summary

An attempt was made to investigate the statement that children with mongolism are hypersensitive to atropine. A drop of atropine was placed in the right eye of nineteen mongols and twenty similarly retarded children without mongolism. The mongols tended to react more quickly, and their reaction was sustained longer. The difference was statistically significant. Further investigation of this phenomenon may throw light on the nature of the defect in mongolism.

We are grateful to the staff of the hospital, and particularly to Dr. M. C. Liu, Dr. E. B. Lind, and Dr. Ajita Chakraborty for their assistance.

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# ABERRANT SPLENIC TISSUE MISTAKEN FOR HYDROCŒLE

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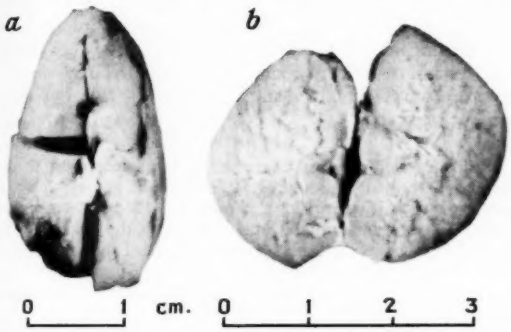
In 1956 Putschar and Manion reviewed all published cases of splenic-gonadal fusion (aberrant splenic tissue in the reproductive organs) and added 4 of their own. Altogether there were 30 cases which could be divided into two distinct groups. In 18 a cord-like structure connected the main spleen and the aberrant tissue, whereas in 12 there was no continuity between the two. Another case of the first type was later described by Daniel (1957). The case we report here belongs to the second group.

A 5-year-old boy of Polish origin was brought to our clinic because his parents had recently noticed a swelling in his left scrotum. He had not complained of any discomfort, and the parents could not recall any recent or remote trauma.

*On examination* he was perfectly normal, apart from the scrotal swelling. This was soft and well-defined; it moved with the testicle; and it was not tender and not attached to the skin. There were no signs of inflammation or of trauma. The inguinal canal appeared normal and no hernia was found.

*On admission* a few weeks later the tumour was not bigger, but it was more elastic. A hydrocœle or a cyst of the lower spermatic cord was suspected; but, on aspiration, only a few drops of red blood were withdrawn. Thereupon we decided to operate.

*Operation.*—Under general anæsthesia the testicle was delivered through a two-inch inguinal incision. The tunica vaginalis was incised. The testicle appeared normal except




**The scrotal spleen: (a) lateral aspect showing ligated hilar vessels, an artery and a vein, and (b) cut surface.**

for a well-encapsulated, dark brown tumour on the lateral side, about a centimetre below the head of the epididymis. The tumour was firmly attached to the testicle by two vessels emerging from a hilum-like formation. The vessels were ligated, and the tumour was removed.

*Pathology*

The specimen was egg-shaped and measured $2\frac{1}{2} \times 2 \times 2$ cm. It had a smooth dark blue capsule, and a slightly depressed hilum on one side; the cut surface was smooth and purple, with many pin-point whitish areas (see figure). Microscopy showed slightly congested but otherwise normal splenic tissue.

Aberrant spleen in the scrotum was diagnosed before operation in only 1 of the cases reviewed by Putschar and Manion (1956); in 29 it was an unexpected finding at operation for inguinal hernia, undescended testicle, or suspected tumour of testicle, or at postmortem examinations. In 5 cases it was accompanied by multiple anomalies—in all cases but 1 these were left-sided. A correct preoperative diagnosis is of little importance, except when splenectomy is indicated for some blood disease (Daniel 1957). In such cases it is essential not to overlook a spleen in this site. The withdrawal of fresh blood from a scrotal tumour or suspected cyst may be caused by puncture of a vessel; but an aberrant spleen should also be kept in mind.

**Summary**

A case of aberrant spleen in the left scrotum, unattached to the main spleen, is reported.

A bloody tap from a punctured scrotal mass should arouse suspicion of aberrant spleen.

We are grateful to Dr. J. Birkhan, head of the department of anæsthesia, for his help.

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# Preliminary Communications

## PURIFICATION OF ASPERGILLIN O

WE have previously reported that one strain of *Aspergillus oryzæ* (B–1273) excels as a producer of a material with high and fairly selective fibrinolytic activity.[1] We have now obtained a purified preparation of the active material.

METHOD

Our process is carried out at room temperature unless otherwise indicated.

The fungus is grown on the liquid medium which we have recently described,[2] in the dark for 5 days, at which time the culture is separated from the medium by filtration through Whatman paper no. 40. The yellow fluid (pH 5·8) is then passed through a column of anion-exchange resin (IRA–400) in the Cl-cycle. The pH is brought from 5·4 to 6·8 by adding 1/10 volume of *N*/10 sodium hydroxide, slowly and with constant stirring (adjusted filtrate). When two volumes of acetone are added, also slowly and with constant stirring, a white flocculate is obtained. After settling overnight at 4°C, the suspension is centrifuged at 1000 r.p.m. for 10 minutes. The supernatant is discarded, and the precipitate is dried for one hour under aspiration. It is then resuspended in a volume of distilled water equal to 1/10 of the original adjusted filtrate. The suspension is passed through Whatman paper no. 50 to separate insoluble material. Further purification may be obtained by adding 1/10 volume of 1% solution of $CuSO_4.5H_2O$ $ZnSO4.7H_2O$ $3CdSO_4.8H_2O$, which causes the precipitation of large amounts of impurities without much loss of activity. The supernatant is dialysed in Visking bags (V-41-2) against frequently changed distilled water for 22 hours, and then it is lyophilised overnight. The final material is whitish, fluffy in appearance, and hygroscopic. The ordinary yield is 75–150 mg. per litre of filtrate media.

PROPERTIES

The purified material is soluble in water (27 mg. per ml. at room temperature) but insoluble in alcohol, acetone, and other fat solvents. It may be recovered from mixture with these fat solvents, after their evaporation, without loss of activity in the case of ether, petroleum ether, acetone, and ethyl alcohol; but with complete loss of activity in the case of methyl alcohol. A water solution is active up to 50°C, and has optimum activity at pH 7·6, with gradually diminishing activity down to pH 4·5 and up to pH 11. The material is precipitated from solutions with only relative loss of activity by tannic acid, and is not precipitated by boric, molybdic, or benzoic acids; it is partially absorbed by $BaSO_4$ and by alumina gel.

Some chemical properties have been ascertained. The material shows a peak of optical density at 2800 Å. There is clouding when a solution is treated with trichloracetic acid. The substance gives a positive phenol reaction, a positive bromine test for unsaturated bonds, negative test for pentoses, and negative iodine test for simple polysaccharides. Hexuronic acid is present. Organic phosphorus and sulphur are absent. Analysis shows the average composition to be 65% hexose, 6% inorganic phosphorus, and 3% nitrogen. Na and Cl are present in equimolecular proportion as NaCl. Ash represents 15%. The material has low toxicity ($L.D._{50}$ for rabbits is higher than 200 mg. per kg.), and no antigenicity has been demonstrated in guineapigs, rabbits, and dogs. Activity experiments using standard techniques show that the purified material digests bovine and human fibrin heated (Astrup) plates at a dose as low as 0·097 µg. Against unheated plates, it acts more slowly but more strongly. Its effect is directly lytic as the substance is not an activator of the fibrinolytic system. Although a strong inhibitor is found in human plasma and serum, the material acts against human and dog plasma clots, especially if added after the clot has formed. Its activity, especially against human

1. Stefanini, M., Marin, H. *Proc. Soc. exp. Biol., N.Y.* 1958, **99**, 504.
2. Horace, J., Stefanini, M. *ibid.* (in the press).

fibrin, is greatly enhanced by heparin. In experiments where it is present at a final concentration of 100 μg. the substance is active against casein, egg albumin, denatured human hæmoglobin, tosylarginine methyl-ester, and benzoyl-arginine methyl ester, and it is inactive against normal human hæmoglobin. Its activity is not disturbed by soya-bean inhibitor, δ-amino n-valeric acid, and protamine sulphate, and only slightly by ε-amino n-caproic acid. The material accelerates slightly the in-vitro generation of thromboplastin and thrombin. On incubation with plasma, it shows strong anticoagulant (antithrombic) activity. Plasma recalcification time is greatly prolonged. The following coagulation factors appear to be destroyed or inhibited in order of decreasing susceptibility: fibrinogen, labile factor (factor V), prothrombin, and stable factors (factor VII). Antihæmophilic globulin, plasma thromboplastic component (Christmas factor), and Hageman and Stuart factors are relatively resistant to the action of the substance, which, at a concentration of 1 mg. per ml., demonstrates lipolytic activity in plasma.

### USES

The material has been tentatively named Aspergillin O, and has been used in the control of experimental thromboembolism in dogs and in selected cases of thromboembolism in man.

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## THE ACTION OF CHELATING AGENTS IN WILSON'S DISEASE

ONE of the main difficulties in assessing the role of copper in the pathogenesis of Wilson's disease (hepatolenticular degeneration) is the poor correlation between the observed clinical response and the cupruresis which follows the administration of chelating agents. This has been commented on recently by several authors.[1–3] In considering the possible mechanisms of copper toxicity one of us (J. M. W.), in an earlier publication,[4] suggested that copper might block sulphydryl groups which are present on the enzymes of the Krebs cycle, thereby interfering with energy supplies at the cellular level. The possible beneficial role of dimercaprol (BAL), and presumably penicillamine, in Wilson's disease might then be due to their ability to supply readily available –SH groups for intermediary metabolism.[3] In arsenical poisoning the trivalent metal blocks the dithiol lipoic acid, and requires a dithiol, BAL, to open the ring compound so formed.[5] Since a monothiol, such as penicillamine, is able to mobilise copper in Wilson's disease, the block is likely to be to a monothiol, such as the –SH group on reduced cœnzyme A. If a large number of these groupings were to become blocked by a divalent metal, such as copper, this would interfere with the entry of pyruvate into the Krebs cycle and lead to an accumulation of the ketoacid in the blood.

There is little in the literature concerning pyruvate metabolism in Wilson's disease. Although Cumings[6] reported studies on two patients he was unable to demonstrate any action of BAL on pyruvate tolerance. But this evidence did not seem to us sufficient to justify the conclusion that pyruvate metabolism is never abnormal in Wilson's disease, and we decided to reinvestigate this and the possible effect of other sulphydryl compounds upon any abnormality detected. As controls we made similar investigations on patients with hepatic cirrhosis with abnormal pyruvate-tolerance tests.

### CLINICAL MATERIAL

We studied three patients with Wilson's disease—case 1, a man aged 20, who had been treated with penicillamine for 2 years and with BAL for several months before that; case 2, a man of 21, had had no previous therapy; and case 3, a girl of 13, who had had penicillamine for 4 months before the present study. In cases 1 and 3 penicillamine was discontinued for 3 weeks before any tests were made. Our control cases were a man of 62 with cirrhosis secondary to chronic alcoholism, and a man of 46 with progressive chronic hepatitis.

### METHODS

Pyruvate-tolerance tests were carried out according to the method described by Joiner et al.[7] in which glucose 50 g. is given at zero time and again at 30 minutes. Blood was taken for pyruvate estimations at 0, 60, and 90 minutes, the method being that of Friedemann and Haugen.[8] In some of the tests lactate was estimated by the method of Barker and Summerson.[9] All the patients were given thiamine 100 mg. before the investigations were started.

### RESULTS

*Wilson's Disease*

CASE 1.—Because pyruvate and lactate tolerance was at the upper limit of normal,[7] no further studies were made.

CASE 2.—The fasting blood-pyruvate and the figures for 60 and 90 minutes were high before treatment, but were brought within the normal range by 3 days' treatment with penicillamine, 900 mg. daily.

CASE 3.—Before treatment pyruvate and lactate tolerance was grossly abnormal, but it returned to the upper limit of normal after penicillamine 900 mg. had been given daily for 3 days. It took a further 2 weeks before the tolerance tests reverted to the pretreatment level. A second course of penicillamine again caused the pyruvate and lactate tolerance to return to normal, and, on a later occasion, the same effect was obtained with N-acetyl penicillamine.

*Controls*

Both cases of hepatic cirrhosis had abnormal pyruvate tolerance, and in neither was this in any way influenced by treatment with penicillamine.

### CONCLUSIONS

The evidence presented here underlines the difference between the metabolic disturbance of pyruvate utilisation in Wilson's disease and hepatic cirrhosis of other ætiologies. In doing so, it supports the hypothesis that copper plays an important part in the pathogenesis of Wilson's disease. The ability of N-acetyl penicillamine to correct the abnormal pyruvate metabolism in Wilson's disease is of importance because, unlike penicillamine, the N-acetyl derivative does not mobilise copper in the urine. The evidence, therefore, also supports the theory that the beneficial action of chelating agents in Wilson's disease may

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9. Barker, S. B., Summerson, W. H. S. *ibid.* 1941, **138**, 535.

be, at least in part, associated with their ability to supply alternative –SH groups for intermediary metabolism.

We think that our first patient with Wilson's disease (case 1) showed no abnormality of pyruvate metabolism because he had had a long " de-coppering ", first with BAL and later with penicillamine, and this resulted in an adequate supply of –SH groups which was not significantly depleted by 3 weeks' withdrawal of treatment. In support of this explanation is the observation that in case 3 only 3 days' penicillamine corrected the pyruvate metabolism which then took 2 weeks to revert to its initial abnormal state.

We hope later to publish details of the present investigation and further studies of the action of BAL, other sulphydryl compounds, and edetic acid (' Versene ') in Wilson's disease. If our hypothesis is correct edetic acid, though able to mobilise copper, should not be able to correct pyruvate metabolism, because it does not possess sulphydryl groups in its molecule.

We wish to thank Dr. S. Nevin, Dr. H. G. Morgan, and Dr. T. C. Meyer for referring their patients with Wilson's disease for these investigations, and Dr. A. P. Dick for letting us study one of his patients with hepatic cirrhosis.

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## New Inventions

### AN IMPROVED BOX FOR THE STERILISATION OF DRESSINGS

RECENT reports from a Medical Research Council working party [1] and from the Nuffield Trust [2] have aroused great interest in the choice of suitable containers for sterilising equipment in general hospital use. But little attention has been paid to the filter dressing box. Boxes of this type have fabric filters that will allow the passage of steam but not of bacteria; they are used in many European hospitals but are relatively uncommon here. A recently designed dressing box, with several novel features, has been tested experimentally, and compared in routine practice with the containers in general use.

*a*

*b*

**(a) Box with lid open showing the oversize filter exactly fitting the inside of the lid, and the method of fixing the clamping plate.**
**(b) Outside view showing perforations in the lid, and the arrangement of fasteners and feet.**

The prototype box was manufactured from heavy gauge copper, with welded seams, and a wire beaded top to give greater rigidity (see figure). It measures $12 \times 10 \times 8$ in.—the same dimensions as the large conventional box used in this hospital. All the corners and edges are rounded because this makes them stronger than sharp edges and square corners. The bottom and lid are each perforated by 1216 holes, of $^1/_8$ in. diameter and evenly spaced, to allow rapid steam penetration and air release through the filter. Perforated plates with a $^3/_4$ in. plain rim are used to clamp suitable filter material inside the lid and bottom. The fixing screws have knurled nuts and penny slots so that the filters can be changed without special tools. The filter material for the bottom is cut to the exact size of the outer edge of the clamping plate, minimum perforation is made for the fixing screws, and the frame is then bolted on so that the material is tightly clamped. For the lid the material is cut 2 in. larger all round than the inside of the lid, the excess is folded back to make an accurate fit, and the double layer is fixed by the clamping plate. Thus on closing the lid the material is trapped between the lid and the sides of the box, acting as a seal. When nylon twill is used as the filter material fraying can be prevented by hot sealing, and folding back is unnecessary. A special type of self-adjusting hinge, to allow even closing of the lid on the seal has been fitted, as conventional hinges are strained if so used. The box is fitted with specially designed toggle fasteners, which have stainless-steel spring clips for quick locking and release of the lid, and a central carrying handle. There are four feet, each $^3/_8$ in. high, which serve a dual purpose; they keep the bottom of the box clear of contaminated surfaces, and they facilitate stacking because the bottom of each foot is recessed to fit over studs on the lid of the box below.

#### FILTER MATERIAL

Material used for filters in any box should:

(1) Be of close weave, and sufficiently " fluffy " or thick to prevent the passage of airborne bacteria.

(2) Be easily penetrable by steam. The fibres must not swell so much when wet that the material becomes impenetrable.

(3) Withstand frequent autoclaving at the steam pressures and temperatures in general use without deterioration.

(4) Resist direct contamination by waterborne organisms.

The most satisfactory materials have proved to be heavy cotton twill (15–20 oz. per sq. yard) and heavy nylon twill fabric (10–15 oz. per sq. yard). Cotton twill is relatively cheap but discolours in use, though without apparent ill effect. Synthetic material is considerably more expensive but absorbs little moisture, does not discolour easily, possesses great tensile strength, and is immune to attack by bacteria.

*Experimental Tests*

The ability of cotton twill and nylon twill to resist droplet and dust-borne infection has been extensively tested in specially designed apparatus.[3]

Both types of material (1 in. discs) sterilised by filtration a minimum of 3000 litres of aerosol containing approximately 100 droplet nuclei per litre (average droplet size 3 μ). Similar results were obtained with dustborne particles.

*Practical Tests*

Numerous tests of cotton-twill filters in boxes packed by theatre staff with dressings, towels, &c., and subjected to routine sterilisation in the hospital autoclaves have proved satisfactory. Sterilisation was checked by placing, at various points in the boxes, thermometers and linen squares impregnated with *Bacillus subtilis* spores.

To test the long-term sterility we used the following method.

The empty box was sterilised by autoclaving at 20 lb. pressure for 20 minutes. It was then opened with full bacteriological precautions, and the bottom was lined with 5% horse-blood agar plates, half with exposed surfaces facing upwards and half facing downwards. The box was then closed and placed in the trunking of the forced ventilation system of this institute, between the intake and the filters. As a control a new dressing box with side slides was treated in the same way, except that all the blood-agar plates faced upwards. Several experiments were performed, the boxes being exposed for periods of 8 hours to 2 weeks. On removing them from the trunking they were opened, and the blood-agar plates were removed and incubated at 20°C and 37°C. The results showed that the contents of the filter box regularly remained sterile for 2 weeks (the longest period tested), while the blood-agar plates in the control slide box always showed bacterial contamination in 3–7 days. Blood-agar plates exposed in the trunking were always contaminated after 30 seconds' exposure (average count 16 colonies per plate).

The power of the filter boxes to withstand direct contamination was tested thus:

We poured graded amounts of an overnight broth culture of *Sarcina lutea* on to the outside of the lid over the holes, and swabbed the

1. Medical Research Council: Report by the Working Party on Pressure-steam Sterilisers. *Lancet*, 1959, i, 425.
2. Nuffield Provincial Hospital Trust: Present Sterilising Practice in Six Hospitals. London, 1958.
3. Thompson, R. E. M., O'Grady, F. W. To be published.

inside of the filter after 10 minutes. Both types of twill resisted penetration by up to 0·5 ml. of the culture. 2 drops (0·05 ml.) penetrated a closed slide of a new standard-pattern box, under equivalent conditions.

DISCUSSION

The most obvious advantage of the filter box over the slide box is the elimination of one source of human fallibility—namely the slide.

20% of the standard slide boxes in use in this hospital are inefficient and in need of repair, common faults being splitting at the corners and along the edges, ill-fitting slides and lids, and broken or inefficient catches. The slides of these boxes, which are situated on the front and back and were not designed to bear weight, are particularly vulnerable, as the boxes have to be stacked in the autoclave with the openings in the vertical plane to ensure adequate steam penetration.

Many authorities[4,5] advocate the use of linen-wrapped bundles in place of boxes, and in an ideal set-up, with theatre, central supply, sterilising rooms, and adequate adjacent storage, it may well be that these are the packs of choice. But in most hospitals bundles are carted on dirty trolleys through dirtier corridors, and they must be more liable to contamination than sealed tins.

Cardboard boxes have been suggested as dressing containers.[5] Boxes which are penetrated satisfactorily by steam under pressure make suitable containers for dressings and other material for immediate use, but they are open to the same objections as the linen bundles; they harbour dirt and bacteria, and they cannot be cleaned. We have isolated clostridia from new cardboard boxes of a recommended pattern and we feel that they should never be introduced into theatre suites without previous adequate sterilisation.

We should like to thank Mr. P. Ziegler, who designed the box, and G.U. Sterilizers Ltd., London, N.W.2, who made it.

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4. Walter, C. W. The Aseptic Treatment of Wounds; chap. 7 and 9. New York, 1948.
5. Alder, V. G., Gillespie, W. A. *J. clin. Path.* 1957, **10**, 299.

# Reviews of Books

## Elements of Vital Statistics

B. BENJAMIN, B.SC., PH.D., F.I.A., F.S.S. London: Allen & Unwin. 1959. Pp. 352. 56*s*.

CHANGES in census technique and new methods in demographic analysis appearing in the past thirty years have made a new text on vital statistics a clamant need; and it is a need which Dr. Benjamin's book fills admirably. Although the various measures of population behaviour—such as standardised death-rates, life tables, and fertility-rates—are clearly set out, there is no attempt to present the more sophisticated mathematical forms of analysis. Nor is there any description of the simpler biometric procedures now so fully covered by other textbooks. This volume is primarily directed to a public-health audience, and the examples given of the relevance of vital statistics to epidemiological problems reveal the author's long practical experience in this field. The registration of births, deaths, and marriages is fully discussed, and the history and current practice of census-taking, particularly in this country, completes the basic groundwork for national vital statistical work. The bulk of the text is devoted to the use of infectious-disease notifications, maternal and child-welfare reports, and other routine statistical returns in the control of disease, nationally and locally; and there is a full discussion of ways of assessing the importance of environmental factors in its incidence. Hospital and industrial statistics relating to morbidity are dealt with quite fully, and particular emphasis is given to recent development of systems of disease registration —e.g., of cancer or mental disorder—for the intelligent administration of specialised health services.

For the student in the course for the diploma in public health, this text is perhaps more detailed than he needs for the examination. If, however, he restricts himself to the main thread of the discussion, it should prove an invaluable introduction to the subject. As a reference work on points of detail, it will stand him in good stead in his later work in public health. Certainly, every medical officer of health should possess a copy.

## Psychosomatic Methods in Painless Childbirth

L. CHERTOK, médecin-assistant du Centre de Médecine Psychosomatique de Villefuif. Translated from the 2nd French edition by DENIS LEIGH, M.D. London and New York: Pergamon Press. 1959. Pp. 260. 35*s*.

THIS monograph compares Grantly Dick Read's method of natural childbirth and the Russian "psychoprophylactic preparation of pregnant women for childbirth". It also summarises all that has been written about them in the medical literature, and the bibliography contains 587 references. As many of the papers are in Russian, the brief summaries in the text are especially useful. Professor Chertok describes factually and objectively the two methods, the results obtained with them, and the controversy whether they are basically the same or quite different. Almost as in a detective novel, the reader is kept in suspense, and must wait till the very end before hearing the author's very sound conclusion:

"The two methods, the differences between which are minimal in practice, are based on didactic, physiotherapeutic and psychotherapeutic elements. Read began his work as a result of his fruitful intuition, the researches of Velvovski followed on his experiences of hypnosuggestive analgesia in obstetrics, which had already convinced him of the reality of verbal analgesia. The two methods are both effective; their theoretical bases are unclear and controversial. Without minimising the role of didactic and physiotherapeutic factors, the psychotherapeutic factor is of most importance in the production of the analgesia, and is at work at all the stages of the method."

Professor Chertok offers a realistic and fair assessment of a subject on which the average doctor cannot be expected to read more than a fraction of what has been written. But it is a subject which is important to his patients.

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**Red Cross International and the Strategy of Peace** (London: Hodder & Stoughton. 1959. Pp. 270. 25*s*.).—On June 24, 1859, the French and Austrian armies met in battle at Solferino in Northern Italy. By nightfall 40,000 men lay dead or wounded, tended only by hopelessly inadequate medical services. Henri Dunant, a wealthy Swiss financier, had been an unwilling witness of the battle, and he was so moved by the desperate straits of the wounded that he spent the rest of his life trying to help casualties and prisoners all over the world. This story of how the International Red Cross was started is well known, but Mr. J. A. Joyce, writing for its centenary, also describes in detail its early days, its organisation, and some of its multiple activities, and he has made the book more than a mere history. Written into it is a plea for the resolution of that paradox in human nature on which the whole movement depends. The motto of the International Red Cross is *Inter Arma Caritas*, which may be rendered as "charity even on the battlefield". When the true connotation of charity is universally recognised, there shall be no more battlefields.

**Parsons' Diseases of the Eye** (13th ed. London: J. & A. Churchill. 1959. Pp. 613. 50*s*.).—For its latest edition this popular textbook has been extensively revised and rearranged under the editorship of Sir Stewart Duke-Elder, but its general character remains unaltered. It continues to provide for the student and practitioner a reliable guide to diseases of the eyes.

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## New Thoughts on Leukæmia

MOST people think of leukæmia as a type of malignancy. But this idea has not been universally accepted or fully substantiated. Leukæmia in fowls can be caused by a transmissible virus, and there is evidence that in mice the disease can be induced indirectly by virus infection.[1]

In our last issue Dr. N. H. D. SCHÖYER put forward a hypothesis based on the proposition that cells have " a natural tendency to continuous multiplication, which in multicellular organisms has to be restrained ", and that the restraining is done by inhibitory substances in the circulating blood. There are, he suggests, two ways in which inhibition may fail: (1) the inhibitor may be absent or deficient, or (2) the cells may be unable to react to it properly because damage to the nucleus has injured the genes, or complex of genes, on which it acts. The first abnormality leads to proliferation of cells in many sites at once, and at first this sort of proliferation can be controlled by administering the missing inhibitor; but long-continued deficiency may cause genetic changes in the cells and then the proliferation becomes that of the second type. This second type corresponds to the familiar local autonomous growth in malignancy and is due to damage to the " receiving genes " by chemicals, physical agents such as X rays, or biological agents such as viruses. The greater the damage, the less the susceptibility to normal inhibitors and the more rapid the growth.

On SCHÖYER's hypothesis the chronic leukæmias are examples of the first type of abnormality, whose primary cause is deficiency of inhibitor; and to show that they may respond when his hypothetical inhibitor is supplied he adduces evidence from two sources. First he cites experience at Leipzig where repeated blood-transfusions are said to have restored the white-cell count to normal in about half the treated cases of chronic myeloid and chronic lymphatic leukæmia—the same effect being obtainable with liquid plasma but not with washed cells, nor with gamma-globulin. Secondly, he describes the behaviour of leukæmic cells in tissue culture. ISRAËLS,[2] in 1940, reported that, when they were cultured in normal plasma, leukæmic leucocytes would mature—at any rate as far as the metamyelocyte stage in the granulocyte series. SCHÖYER quotes in detail similar results obtained lately by SWAEN. He interprets both these groups of results as showing that, if the plasma inhibitor is present, normal growth will be restored. What the nature of this inhibitor is he does not know, but he hopes that trials of plasma fractions will yield the answer.

1. See *Lancet*, 1958, ii, 30.
2. Israëls, M. C. G. *J. Path. Bact.* 1940, **51**, 235.

Acute leukæmias are held to differ both in ætiology and character from chronic leukæmias; for here the primary lesion is damage to " receiving genes ". SCHÖYER quotes no direct evidence for this suggestion; but, since his paper was first submitted to us more than a year ago, support has come from studies on chromosomal abnormalities in leukæmia. FORD, JACOBS, and LAJTHA [3] devised a technique for studying the chromosomes in human bone-marrow. In nine of the twelve leukæmic marrows which they examined the frequency of mitosis was so low that no reliable observations could be made, but in one of the other three cases most of the cells were clearly abnormal and contained 44 chromosomes, as compared with the now accepted normal of 46, plus an additional minute fragment. On p. 425 we publish further studies by BAIKIE, COURT BROWN, JACOBS, and MILNE of chromosomes in human leukæmia: in acute leukæmia, chromosome abnormalities were found in four out of five cases, whereas none were detected in five cases of chronic myeloid leukæmia, one of chronic lymphatic leukæmia, and two of myelomatosis. The case reported in detail was atypical in several respects, and further investigations will be welcome; but their findings lead Dr. BAIKIE and his colleagues to discuss whether there is an essential difference between the acute and chronic forms of leukæmia, " either in their mechanisms of induction or in their pathogenesis ". Their evidence, though not yet complete, fits the idea that " acute leukæmias are the result of changes in the genetic material of the cell ", and so supports this part of Dr. SCHÖYER's thesis. Since chromosome study by the method of FORD et al. is reasonably simple, much further information will no doubt soon be forthcoming. Studies should include typical examples of the recognised types of acute leukæmia, because there may well be differences between such easily distinguishable types as acute lymphatic and acute monocytic leukæmia. Another important point to be borne in mind is that chromosome abnormalities may occur in other proliferative states in the bone-marrow. For instance, FORD et al. record that in one case of pernicious anæmia 35% of the mitotic cells had fewer than 46 chromosomes, and pernicious anæmia is not a malignant disease but a vitamin deficiency.

## Explanation on Conviction?

OFFENCES against the criminal laws of this country may be punished by fine or imprisonment or, in some few cases, by death. The number of such offences is considerable and is increasing. Nevertheless, the criminal laws do not cover by any means all forms of immoral or illegal conduct. Their scope is in fact somewhat arbitrary. They operate against, on the one hand, acts which civilised communities condemn—for instance, murder, personal assaults, and theft—and, on the other hand, acts which Parliament has decided shall be punishable in the interests of public safety or in order to enforce the activities of the State in economic planning and social welfare. Most people would regard it as prudent to comply with this second group of laws, but not all

3. Ford, C. E., Jacobs, P. A., Lajtha, L. G. *Nature, Lond.* 1958, **181**, 1565.

would regard compliance as a moral issue. Whereas society is almost unanimous in designating the thief as "criminal", many would not describe in this way a person convicted of dangerous driving. But, despite conflicting attitudes, most people would probably agree that in the public interest the State must have the right to punish offences covered by the criminal laws. (This right will not necessarily be exercised; a wise magistracy will always consider the individual and deal with some offenders by probation and similar methods.)

In a letter which we published a fortnight ago, Dr. BARTON HALL [1] made the interesting suggestion that society has the right, in addition to that of punishment, to an explanation from the wrongdoer: just as the bankrupt must explain to his creditors how his conduct of his affairs has contributed to his difficulties, so the wrongdoer should be called to account for his behaviour. The analogy is, of course, not complete. The bankrupt has of his own free will entered into a special relationship with his creditors in that he has borrowed money from them or has obtained goods or services on credit; and at his examination he is seeking to be released, at least partly, from his obligations. These special considerations do not normally enter into the criminal law. Nevertheless, each citizen has obligations to the community of which he is a member and whose benefits he accepts. If he breaks its laws, it would not be unreasonable to ask him to explain his conduct—though this explanation could be called for only after conviction.

Dr. BARTON HALL suggests that such a procedure would provide an opportunity of collecting information on the response of prisoners in a test situation. We certainly need a great deal more information of a type which can only be collected from prisoners themselves about the causes of crime, and the course suggested by Dr. BARTON HALL might be one way of obtaining it; but other methods, such as that adopted by Lord Pakenham [2], may prove more effective. Before the duties of the Courts were extended into a new field, there would have to be evidence that the work involved would be justified in terms of results.

Dr. BARTON HALL suggests, too, that the response of the prisoner could be taken into account in determining sentence. One difficulty here is that the prisoner may continue to assert his innocence or even say nothing at all. Since he could hardly be given added punishment on that account, silence might seem to him the safer course lest he said anything detrimental to his interest. In any event, judges would still have other methods of obtaining information about the prisoner and his state of mind. Notably, they can remand for a report. Perhaps greater use should be made of these methods, which are likely to be more reliable than statements made by the accused in open court when awaiting sentence. Dr. BARTON HALL draws attention to the possible deterrent value of convicted persons having to explain their conduct publicly. This seems rather speculative. If the fear of detection and punishment does not deter, it is doubtful whether the duty to explain would do so, particularly as it could be evaded by silence.

If such a procedure were introduced, it could hardly be applied to the hundreds of offences which come daily before the magistrates. It would be presumably limited to cases tried at assizes or sessions. This would create some anomalies. The person who elected to be tried summarily for dangerous driving would escape the responsibility of giving an explanation; but the man who elected to be tried for this offence by a jury would have to give an explanation.

1. Barton Hall, S. *Lancet*, Sept. 12, 1959, p. 349.
2. Lord Pakenham. The Causes of Crime. London, 1958. See *Lancet*, 1958, ii, 77, 79.

## Human Chromosomal Abnormalities

Many of those who attended the first symposium on Nuclear Sex at King's College Hospital, London, two years ago [1] met there again last week with some new colleagues to discuss human chromosomal abnormalities. The two subjects might at first seem not very closely related; but the number of people who have been led by interest in the one to study the other is remarkable, and there is no doubt that the original symposium, by bringing together representatives of diverse disciplines who have since been able to collaborate very happily, played some part in securing for this country its present lead in human chromosome studies.

The three main successes in this field are already fairly well known.[2] Mongolism depends on the presence of a single extra chromosome, a third member of one of the two smallest autosome pairs. Chromatin-positive Klinefelter's syndrome depends on the presence of an extra sex chromosome, two Xs and one Y being constantly found. Thus in these two there are 47 chromosomes—one more than the normal 46. In chromatin-negative Turner's syndrome one sex chromosome is missing, there being only one X and no Y, and the total count is 45.

Most speakers at the conference confined themselves to various aspects of these three conditions, but two new chromosomal anomalies were described. Miss PATRICIA JACOBS, of the M.R.C. Group for Research into the General Effects of Radiation, described an example of what, on the analogy with Drosophila nomenclature, she calls a "super female"; the patient proved to be XXX on both marrow and skin cultures. Though this woman (whose case is discussed by Miss JACOBS and her colleagues in an article on p. 423 of this issue) had oligomenorrhœa and some hypoplasia of uterus and ovaries, and her intelligence was below average, the total disorder was surprisingly slight. Duplication of the sex chromatin in some oral mucosal cells raised the possibility of relatively easy detection of further cases. In addition to this case Dr. L. LEJEUNE (Paris) reported a case of polydysspondylism (a child with dwarfing, low intelligence, and multiple malformations of spine and sella turcica) in which only 45 separate chromosomes were present, one of the smaller chromosomes having apparently become attached by translocation to one of the medium-size chromosomes.

1. *Lancet*, 1957, ii, 628, 637.
2. *ibid.* 1959, i 715.

Apparently the origin of changes of the kind met with in all these anomalies except the last is most probably non-disjunction in the parental gonads—that is to say, the process whereby, in the case of the sex chromosomes, pairs of spermatozoa are produced in which, instead of there being an X in one and a Y in the other, there is an XY in one and an O in the other, and a corresponding pair of ova may be produced which are not both X, but one XX and the other O. Obviously an XXY Klinefelter's zygote could be produced by union between a non-disjunctive XX ovum and a normal Y spermatozoon, or between a normal X ovum and a non-disjunctive XY spermatozoon. There was an animated debate on the details—whether, for instance, the non-disjunction occurs at first or second meiotic division (or both) and whether it is usually maternal or paternal (or, again, both). Argument centred especially round the colour-blindness data in Turner's and Klinefelter's syndrome provided by Dr. P. E. POLANI, Prof. H. NOWAKOWSKI (Hamburg), and Dr. J. S. S. STEWART. Some cases were presented in which colour-blindness in XO Turner's syndrome had quite clearly been inherited through the mother, and the single X must have come from the ovum; therefore no sex chromosome at all could have been inherited from the father, and the disjunction must have been paternal. From similar evidence maternal non-disjunction is exceedingly probable in XXY Klinefelter's syndrome. Evidence for the contrary process in each case would be much harder to find, but on the whole it seems likely that maternal and paternal defects can be responsible in both syndromes.

Non-disjunction seems to increase in frequency with the age of the gonad, though the experimental evidence for this widely accepted view is apparently not very good. Prof. L. S. PENROSE reviewed the very striking effect of maternal age on the incidence of mongolism, and showed that a similar though much less pronounced effect is present in both Klinefelter's and Turner's syndromes—though with the present incomplete data on these conditions they could equally readily be explained as effects of paternal age or birth order. He made a plea for the collection, in all cases of possible chromosomal anomalies, of such data as family history, maternal age at birth, and presence of such marker lesions as colour-blindness.

Dr. C. E. FORD discussed mosaics. He believes that certainly in one case of Turner's syndrome and possibly in two others he can detect two races of cells in the marrow—one normal 46/XX, one abnormal 45/XO. These two were seen in the marrow; skin cultures were in every case pure 45/XO. He suggested that in some cases the original embryo may have been pure XO, but that at some stage a somatic non-disjunction had led to the appearance of a race of normal XX cells: such cells, being perhaps fractionally more viable than the XO cells, might be supposed to establish themselves among, and in time possibly even to outgrow, their hosts in the relatively labile and mobile cells of the marrow, though not in the fixed tissues. But the subject of mosaics is obviously one on which there is an acute difference of opinion.

Dr. BERNARD LENNOX showed that testicular feminisation, last of the three so-called " sex-reversals " revealed by nuclear-sexing methods, does not depend on any chromosomal anomaly, each of four cases being simple 46/XY: this despite the fact that it has been attributed to a chromosomal abnormality more generally than either of the other two, in which such a lesion has now been demonstrated. Dr. URSULA MITTWOCH sought to explain the low counts of polymorph drumsticks in XXY Klinefelter's syndrome on a basis of imperfect lobing of the polymorph; but Dr. W. M. DAVIDSON denied this. He also reviewed the evidence for the relation of the drumstick to the sex chromatin, and put forward the interesting hypothesis that the XX heterochromatin, having no function in the post-mitotic cell, tends to be aggregated and in the extreme case of the polymorph extruded from the nucleus.

Dr. W. M. COURT BROWN described the findings in marrow counts of the chromosomes in leukæmia. In chronic lymphatic and myeloid leukæmia, the counts were consistently normal. In four out of five cases of acute leukæmia in adults, however, anomalies were present—abnormalities of number in two, translocations with normal numbers in two. (This accords with the findings of Dr. BAIKIE and his colleagues, whose report appears on p. 425.) In one case of leukæmia in a mongol the leukæmia cells showed the same abnormality of chromosome number as the normal tissues. In addition one radiation-induced acute leukæmia from his ankylosing-spondylitis series showed a modal number of 42; and there were also many polyploid cells, with multiples of 21 preponderating. A further case studied over a period of months showed at first a modal number of 48, with a shift late in the course of the disease to 47, and the suggestion of the appearance terminally in an irradiated area of bone of a race of cells with a modal number of 49. Dr. COURT BROWN also announced the setting up in Edinburgh of a registry of chromosome anomalies, to cover as far as possible all such cases in Scotland and the Newcastle area. The intention is primarily to accumulate over the years data on the mortality of these cases, with emphasis on their prospect of survival and their cancer mortality. It is already known that mongols have a raised incidence of leukæmia, and there could very well be some similar abnormal incidence in other chromosome anomalies.

A subject very much in the forefront is the problem of finding suitable new subjects for investigation. Dr. D. G. HARNDEN, using both his own material and a valuable compilation of other workers' results—especially those of Dr. LEJEUNE and of Dr. M. FRACCARO (Uppsala)—was able to gather a fairly impressive list of negative findings—such likely disorders as anencephaly, epiloia, Laurence-Moon-Biedl syndrome, neurofibromatosis, arachnodactyly, osteogenesis imperfecta, and achondroplasia are already at least in part eliminated. Dr. FORD's final summing up gathered together some views on this point. It seems likely that major anomalies of the larger chromosomes (except the X) are usually lethal,

and so will be found, if at all, only in early spontaneous abortions. Most of the conditions so far recognised involve trisomy—the addition of an extra member to a chromosome pair—XXY, XXX, and mongolism. In two of these cases the extra chromosome is one of the smallest. In the "super female" it is an X, and the body is clearly unusually tolerant to variations in the number of Xs (otherwise the difference in viability between the sexes would be much greater than it is). In Turner's syndrome there is loss of one chromosome; and again it is one of the smallest, and fairly certainly the least important, of all the chromosomes—the Y—that is involved (though the very profound effects it is able to produce in XXY Klinefelter's syndrome show that even the Y is not the inert marker it has sometimes been supposed to be). There are a few other theoretical possibilities—trisomy of the one remaining small chromosome pair, loss of a member of either of the two non-Y small pairs, or XYY—but none of these is very likely. There may be many more examples to be found of irregular lesions such as the translocation found in Dr. Lejeune's case of polydysspondylism; but these are probably unique events, accidents producing congenital disability of some form and by some means that may never be reproduced. Yet even such unique events may afford a clue to the functioning of individual chromosomes. As techniques improve, smaller and smaller defects of this type should be recognisable, and there is clearly a case for examining almost every case of atypical congenital defect, particularly if more than one system of the body is involved. Even in the conditions in which negative results have been found, larger series of cases must be examined: for instance, simply because a few cases of epiloia have proved not to be due to any recognisable chromosomal anomaly this is not necessarily true of all cases. The easiest successes may have already been won, but a great deal of work remains to be done.

# Annotations

## NEW LIVER FUNCTION TESTS

THE use and limitations of laboratory tests of liver function have been widely and intensively discussed for many years, and it is doubtful whether modification of existing tests will much increase their value. A possible exception is the modification of the rose-bengal excretion test introduced by Nordyke and Blahd.[1] Rose bengal was one of the first dyes to be used to test the excretory function of the liver, but it has been almost entirely superseded for this purpose by sulphobromophthalein, which is much less toxic and can be detected even in low concentrations by the purple colour that it develops in alkaline solution. In 1955 Taplin et al.[2] published their results with rose bengal that had been made radioactive with $^{131}I$ by an ion-exchange reaction. The excretion of this dye by the liver was assessed by means of a scintillation counter placed on the abdomen in the area of the liver. As Nordyke and Blahd point out, however, the situation over the liver is extremely complex, functions occurring there simultaneously that may result in "increases, decreases or variable changes in radioactivity beneath the probe"—for example, uptake of dye by the parenchymal cells, variations in hepatic blood-flow, pooling of dye in the biliary passages, and excretion into the intestine. To avoid these and other possible variables they have chosen the head as the site to which to apply the scintillation counter, and the consistency of their results confirms the wisdom of their choice.

The test, as recommended by Nordyke and Blahd, is extremely simple. A solution in 2–5 ml. of isotonic saline of 0·1–1·0 mg. of the radioactive dye containing 10–25 $\mu c$ of $^{131}I$ is injected intravenously and counts are made at short intervals for 20 minutes. The result is expressed as the percentage of the activity determined after 5 minutes that is still present after 20 minutes. In 95 healthy subjects the values so determined lay between 39 and 51%. Of 105 patients with diverse liver diseases the great majority gave higher figures for dye retention than the highest figure found among the controls. Thus, in a small series of alcoholics without evidence of cirrhosis, excessive dye retention was found in more than half, while almost all alcoholics with cirrhosis showed impaired dye excretion, retention ranging between 48 and 96%.

The two outstanding advantages of the radioactive rose-bengal test over the sulphobromophthalein test are its applicability to jaundiced patients and the virtual elimination of toxic hazards owing to the minute quantities used. A further advantage is the possibility, by simultaneous counting over the head and the abdomen below the liver, of differentiating between the removal of the dye from the blood by the parenchymal liver cells and its flow into the intestine via the biliary passages. The results of studies with this combined technique might really justify the small but nevertheless real risk entailed in exposing patients to minute doses of radioactive substances.

In these columns Roman and Dulmanis[3] have lately described their experience with estimation of serum quinine oxidase, which they find to be a sensitive and specific index of parenchymatous liver damage. Their early results are impressive, and the test clearly deserves wide trial.

## INFECTIOUS CROUP

IN 1955, Chanock[4] in the U.S.A. and Beale et al.[5] in Canada recovered a virus from cases of infectious croup of childhood, or acute laryngotracheobronchitis. The virus was called croup-associated (or C.A.) virus and was at first found in quite a large proportion of children with croup. No bacterial pathogens have been identified in regular association with croup, and chemotherapy is largely ineffective; so a viral cause is likely. But recently the C.A. virus has not been isolated so frequently, and now Vargosko et al.[6] report the recovery of other respiratory viruses from cases of croup.

47 children with croup from Washington, D.C., were studied for a year, and viruses were isolated from 16. Serological study of 38 of the children revealed viral infection in 27. The viruses implicated were influenza

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virus (Asian variety of virus A), hæmadsorption viruses types 1 and 2 [7 8] (recently classified *Myxovirus parainfluenzæ* 3 and 1 respectively [9]), and sporadic infections with adenovirus and croup-associated virus. The hæmadsorption type-2 virus was the most frequent, being found in 36% of all patients with croup, compared with 2% of a large group of control children who were free of respiratory-tract illness but who showed serological evidence of infection with this or a related virus. Influenza-A virus was not isolated from infants or children with croup, but serological studies showed a suggestive association of this virus with croup (5 out of 14 infections). But unfortunately the controls (15 patients) showed no evidence of infection during October, 1957—the epidemic period for Asian influenza in the Washington area, when some cases would have been expected. Hence the degree of association of influenza viruses with croup remains uncertain.

The impression left by this work is that infectious croup may be a response of some infants and children to infection with several different respiratory viruses. If this is true it is depressing news, since prevention or treatment directed towards the ætiological agent would have little effect at present. In a disease which is so uncommon, in relation to the population at risk, the use of a polyvalent viral vaccine is unlikely to show dramatic results. Yet every effort is needed to combat this illness, which is still one of the dangerous emergencies of infancy and childhood.

## HYDRODYNAMICS OF INFANT FEEDING

THE bottle teat has evolved a long way since rubber first became easily available. The early shape is still to be seen on dolls' bottles; then the next, with a larger capacity, gave way to those with spheroidal bulges at the end; and the pattern subsequently reverted to straighter sides. The designers, who influence the peace of so many homes, are anonymous and their theories undeclared. Almost the first careful analysis of how a baby gets the milk has been made by Ardran and Kemp.[10] In studies using cineradiography and pressure gauges they have shown that a lamb, feeding from its mother or from a veterinary bottle teat, compresses and occludes part of the milk-holding zone of either mamma or teat with the front of the mouth (jaws and tongue), and a rapidly moving depression in the tongue creates suction in the back of the mouth, being followed by a raised area which impels the milk down into the œsophagus. A lamb can even drink the milk from a bottle placed on the floor if the teat is connected to a tube going to the bottom of the bottle.

The processes in a baby's mouth are similar; but the breast has, of course, no teat sinus and does not permit the same observations. The bottle teats studied were too stiff for the baby to occlude the neck, so when the raised tongue compressed the other end of the teat the milk tended to flow back into the bottle. Ardran and Kemp have confirmed Gunther's [11] observation that some babies develop a negative pressure of 200, and rarely even 250, mm. Hg at the back of the mouth. But this suction is less important than the size of the hole in the teat in making the milk flow through it. Most kinds of teats available at present seem not to call upon the tongue's full natural activity but mainly to permit a flow of milk through a hole. The manufacturers have to provide a teat rigid enough to be thrust into the mouth of a small baby too weak to draw its mother's breast into its mouth; resilient enough to refill from the bottle; firm enough to give the baby the feeling it expects in its mouth, and yet so lightly compressible that the mouth's milking action can operate; and capacious enough to deliver milk for one swallow at each jaw action.

Ardran and Kemp have wondered why, if the mouth is used for developing suction, so much of its volume is occupied at the time of feeding by the tissues of the breast. One possible reason is that strong suction is normally used only to pull the nipple and much of the areola into the mouth. The mandible seems then to be best placed to evoke the draught reflex without which very little milk is obtained. This arrangement, in contrast to straight suction on the nipple, has perhaps had evolutionary value in foiling thieves.

## THE INTRACARDIAC ELECTROCARDIOGRAM

THE cardiac catheter has proved a versatile diagnostic instrument. Pressure measurements may be made, blood samples obtained, and indicator dyes or contrast medium injected through it into the heart or great vessels. By placing a German silver electrode at the distal end of the catheter and connecting it to a fine wire woven into the wall of the catheter, the electrical impulses within the heart can be recorded. Much useful information has been obtained by this simple technique which adds nothing to the complexity or risks of cardiac catheterisation.

In 1950 Kossmann et al.[1] described an extensive study of intracardiac and intravascular potentials in the normal heart. In the pulmonary artery the ventricular complex varied in form according to the position of the electrode and most often showed an rsr′, rs, qRs, or rsR′ pattern, the initial deflection usually being positive. The atrial complex was more variable, the initial deflection varying from predominantly negative to predominantly positive. The T wave was always inverted. In the right ventricle the initial deflection of the QRS complex was usually positive, consisting of a small r wave, followed by a deep S wave and an inverted T wave. As in the pulmonary artery, some slurring of the QRS complex was common. The size of the R wave varied according to the electrode position. In one patient unusually large positive deflections were found in the lower part of the right ventricle near the tricuspid valve. A large late R wave was found in 2 patients in the upper part of the right ventricle. The atrial deflections in the ventricle were usually positive waves of low voltage. The ventricular complex obtained from the right atrium showed initially either a positive or a negative deflection according to the position of the electrode. An initial positive deflection was always simultaneous with the R wave from low in the right ventricle, from the superior vena cava, from the right pulmonary artery, and from the right arm lead. The atrial complex recorded in the right atrium was dipolar and consisted of excitation and recovery portions; multiple deflections in the P wave were encountered, the initial deflection being variably positive or negative. It was thought that the initial negative wave might be due

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to the electrode being near the sinoatrial node and on the active side of the myocardium from the start of atrial excitation. The large, late, positive deflections of the QRS complex which were recorded in right atrium and ventricle in relation to the base of the ventricle were thought to be produced by late activation of the crista supraventricularis. Kossmann et al. compared these intracardiac records with simultaneous extremity and precordial leads.

Hecht and Woodbury,[2] after studying atrial excitation with the cardiac-catheter electrode, reaffirmed the dipole concept of cardiac excitation, and claimed that the broad biphasic "mitral" P wave represents left atrial hypertrophy but that the peaked augmented "pulmonary" P wave may be due to cardiac rotation rather than to right atrial hypertrophy. Nevertheless the appearance of such P waves with the onset of congestive heart-failure and their regression with recovery suggests that dilatation or enlargement of the right atrium may be the cause. Moreover, the "right atrial" P wave still has value in clinical assessment of right atrial size and disease —as in pulmonary and right ventricular hypertension and tricuspid stenosis.

The intracardiac electrocardiogram has been used to assist diagnosis in congenital heart-disease. Emslie-Smith et al.[3] showed that in pulmonary stenosis the ventricular complex changed abruptly in amplitude as the electrode passed through the pulmonary valve into the right ventricle. The S wave (which was the dominant deflection) was found to be much larger in the right ventricle than in the pulmonary artery. When recorded simultaneously with pressure tracings, the intracardiac electrocardiogram proved useful in distinguishing valvular from infundibular stenosis, an abrupt change in the complex synchronising with the pressure change in valvular stenosis, and preceding it in infundibular stenosis. Difficulties in interpretation of pressure pulses near the pulmonary valve due to venturi effects might be resolved by a study of the intracardiac electrocardiogram recorded at the same time.

Bertrand et al.[4] have recorded the normal range of patterns and voltages of QRS and P complexes at different sites in the right side of the heart. Although they have not examined the changes in the complexes with different types of cardiac disorder and abnormal pressure-flow relationships, their paper makes several useful points. They find that the shape of the P wave recorded in the right atrium affords a guide to the position of the catheter, the P wave being positive in the lower part, diphasic in the mid part, and negative in the upper. Further studies might show whether variation in the P wave provides a more accurate method of localising the site of the catheter tip in the atrium than fluoroscopy alone. Certainly the method might be very helpful where fluoroscopy is difficult or unsatisfactory.

Recording of the intracardiac electrocardiogram during left-heart catheterisation may differentiate between left ventricular hypertrophy and left bundle-branch block in difficult cases, by showing an initial positive deflection in the left ventricle in the latter.[5]

Intracardiac electrocardiography during catheterisation is a useful safety measure, especially when the coronary sinus is inadvertently entered, for damage to the endocardium has been reported during catheterisation.[6,7] When the injection of indicator dye or contrast medium into the heart is planned, the absence of an injury pattern would confirm that the catheter tip lies freely in the ventricular cavity.

Thus intracardiac electrocardiography may be used increasingly often, not only as a protective measure during cardiac catheterisation, but also in the assessment of right ventricular function, and in the localisation of pulmonary stenosis and perhaps other lesions.

## POLIOMYELITIS STATISTICS

A REVIEW by Martin[8] of poliomyelitis statistics in England and Wales in 1950–57 is specially interesting because in 1950 for the first time poliomyelitis was separated into paralytic and non-paralytic groups in the Registrar General's figures, and because these figures will form a basis for comparison now that vaccination against poliomyelitis has become common. The difficulties of a retrospective comparison are obvious: the incidence of notified poliomyelitis in these eight years varied from 1954 in 1954 to 7752 in 1950. Moreover, the diagnostic criteria which lead clinicians to notify a case as non-paralytic poliomyelitis vary enormously from place to place and from doctor to doctor. In the present series there is no constant ratio of paralytic to non-paralytic cases, and the changes in ratio are not related to the total number of notifications. Many cases notified as non-paralytic poliomyelitis may in fact be cases of non-bacterial meningitis occurring sporadically or in small epidemics. The diagnosis of such cases requires studies beyond the scope of most hospital laboratories, and as the patients recover quickly investigations are commonly not pursued intensively. In considering poliomyelitis it is therefore generally safer to concentrate on notifications of paralytic cases rather than on total notifications.

In almost all age-groups males had a higher incidence of paralytic poliomyelitis and a higher case-mortality than females. The incidence was highest in children under school age (about 240 per 100,000); but the case-mortality has fallen most steeply in this age-group (from 8·9% in 1950 to 1·6% in 1957 in males, and from 6·5 to 1·3% in females). This may be due to wider knowledge of the techniques required to preserve life in the acute stage and to the lessons learned from the Danish epidemic of 1952 in which intermittent positive-pressure respiration was introduced for life-threatening poliomyelitis.[9] In older age-groups, however, no substantial decrease in the case-mortality is evident. In patients over 25 years of age, the average incidence of paralytic poliomyelitis was very much lower (about 91 per 100,000) than in young children, but the case-mortality was enormously higher and decreased much less; the case-mortality averaged nearly 25% for males and nearly 17% for females. These figures indicate the need for vaccination of adults as well as of children, and for regarding every case of paralytic poliomyelitis in an adult as an urgent therapeutic problem. Geographical considerations may be important in deciding whether such a patient should be transferred to a centre specially equipped to deal with life-threatening paralysis. And if the transfer is not made the centre should be informed of the case so that any dangerous developments can be promptly followed by life-saving action.

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## Special Articles

# BEDS FOR CHILDREN IN HOSPITAL

## An Investigation in Newcastle upon Tyne

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PÆDIATRIC beds in many general hospitals and in some children's hospitals are not fully occupied, and so it is said that the need for children's beds in hospital is declining (Balfour 1959, Gairdner 1956). This conclusion is already influencing official policy, but no attempt has been made to find out whether it is true. Most figures purporting to show the numbers of children admitted to hospital show, in fact, only a proportion of such admissions, because official hospital statistics record as " children " only those patients nursed in " pædiatric beds " or in " children's wards "; children nursed in adult wards are not included in such returns. In a survey concerning children in hospital in the Newcastle Region in 1950 it was found that (even excluding those admitted for removal of tonsils and adenoids) only a third were in children's hospitals or pædiatric departments: another third were in isolated children's wards, and the remaining third elsewhere (table I). A more recent investigation by the Division for Architectural Studies of the Nuffield Foundation (Platt 1959), based on fourteen hospital groups in different parts of the country, showed that of 17,830 children in hospital 5073 were in adult wards, and the proportion varied greatly from group to group. It is clear, then, that most official figures showing numbers of children in hospital refer to an unknown and variable fraction—probably on average not more than two-thirds—of the true numbers.

The following facts about the admissions of children to hospital in Newcastle upon Tyne over a period of fifteen years provide, we believe, a sounder basis for assessing bed requirements.

### Finding the Facts

The " need " for children's beds in hospital cannot be measured in any absolute figures. It will vary with a number of factors—the incidence and character of illness, the social conditions of the homes, the treatment available, and (last but not least) the customs of the area as they affect parents, family doctors, and consultants. These factors affect not only the decision whether any given child should be admitted to hospital but also the length of his stay. Thus the need for children's beds may, and we think does, vary from one part of the country to another. What can be measured, and what we are attempting to measure, is any change in this need in a specified area over the past few years. The index we are using is the number of children admitted to hospital. We realise that this index is not in itself a sufficient guide to the number of beds required; but in the light of local conditions it can indicate changes in the need for beds.

TABLE I—CHILDREN IN HOSPITAL IN THE NEWCASTLE REGION IN 1950

| — | Other than tonsillectomy | Tonsillectomy | Total |
|---|---|---|---|
| Children's hospitals and pædiatric departments | 9040 | 1135 | 10,175 |
| Children's wards | 8735 | 8664 | 17,399 |
| Infectious-disease and special hospitals | 6075 | 4022 | 12,597 |
| Adult wards | 2500 | | |
| Totals | 26,350 | 13,821 | 40,171 |

*Definitions*
Children's hospital: a hospital admitting only children.
Pædiatric department: a department in a general hospital under pædiatric supervision admitting medical and surgical illnesses.
Children's ward: a ward for the care of children only; not (or rarely) under pædiatric supervision; usually but not necessarily with a nursing staff for that ward only.
Special hospital: a hospital dealing with one specialty only—e.g., ophthalmology.
Adult ward: a ward where children may be nursed in a general ward with adults or in adjacent siderooms, but nursed by the same staff as the adult patients; not under pædiatric supervision.

Even this figure is not easy to come by. The form SH3 returned annually by each hospital to its regional hospital board classifies admissions (or discharges) according to the specialty of the physician or surgeon under whose care the patient is admitted. Thus, only children admitted under the care of a pædiatrician are classified as " pædiatrics ": all other children are placed in the category of the specialty concerned, and numbered with the adults and not the children. There is, therefore, no way short of a special investigation which will elicit the facts about children admitted to hospital.

In such an investigation it is not sufficient to discover the numbers of children admitted to a given hospital or group of hospitals; for these children may come from differing and possibly fluctuating populations, and changes in neighbouring hospitals may affect their numbers considerably. Instead one must try to trace all the hospital admissions from a given population. Such a survey was undertaken in the city of Newcastle upon Tyne in 1943–44 and again in 1950 (Spence and Taylor 1954) when it was repeated as part of a larger regional survey, the results of which have been communicated to the Newcastle Regional Hospital Board (Taylor, Davison, and Spence 1956). We have now extended this survey to cover the years 1955 and 1957 and made a comparison between the later and earlier figures.

### Method of Study

With very few exceptions, any City of Newcastle child admitted to hospital will go to one of the hospitals in the city, or one of a few hospitals in the immediate vicinity. Our study concerns only City of Newcastle children, and we have sought information for the years 1955 and 1957 on the admissions of all such children under the age of 15 from all the hospitals in the area, whether or not these officially accept children. They have been classified by age and by reason for admission as previously defined (Spence and Taylor 1954). The original investigation of 1943–44 concerned only children under the age of 13; but in the 1950 study the age of acceptance was raised to include those aged 13 and 14, which was felt to be a more useful range, and this age-limit has been retained in the present study. In the original survey admissions to long-stay children's hospitals were excluded, because the beds in these hospitals were at that time quite inadequate for the needs of the area; and, in order to retain strict comparison, we have again excluded admissions to these hospitals. Also, we have excluded admissions for removal of tonsils and adenoids, which were considered separately in the earlier report, because the large numbers in relation to beds occupied distort the general picture, and needs for such beds must be assessed separately (Spence and Taylor 1954).

### The Findings

Table II shows the numbers of Newcastle upon Tyne children admitted to hospital (excluding those for tonsillectomy and those in long-stay hospitals) in our present survey for 1955 and 1957 as against those in previously reported surveys of 1943–44 and 1950. There was a sharp fall in admissions between 1944 and 1950—even more than that recorded, because the 1943–44 admissions were of children up to 13, while the later figures were of children up to 15. However, since 1950 there has been little change. Table III relates the numbers of admissions in 1950, 1955, and 1957 to the size of population studied, and shows that there has been no appreciable change in relation either to the total or the childhood population of the area. In tables IV and V the admissions have been subdivided into age-groups, showing that the fall between 1944 and 1950 did not affect infants under 1 year but both periods above this. Since 1950 figures in the different age-groups have remained stable, both in totals and in relation to the population at risk.

TABLE II—NUMBERS OF NEWCASTLE CHILDREN ADMITTED TO HOSPITAL, 1943–57
(Excluding admissions for tonsillectomy and to long-stay hospitals)

| 1943–44* | 1950 | 1955 | 1957 |
|---|---|---|---|
| 2853 | 2139 | 1989 | 2193 |

* Under 13 years only; remainder under 15.

TABLE III—ADMISSION-RATE FOR NEWCASTLE CHILDREN UNDER 15 YEARS OF AGE

| — | 1950 | 1955 | 1957 |
|---|---|---|---|
| Per 1000 total population | 7·3 | 7·1 | 8·0 |
| Per 1000 population under 15 | 32·5 | 31·1 | 34·2 |

TABLE IV—NUMBER OF ADMISSIONS IN THREE AGE-GROUPS
(Excluding those for tonsillectomy and admitted to long-stay hospitals)

| Age | 1943–44 | 1950 | 1955 | 1957 |
|---|---|---|---|---|
| Under 12 months | 418 | 443 | 470 | 453 |
| 1–4 years | 1048 | 764 | 571 | 650 |
| 5–14 years | 1387* | 932 | 958 | 1090 |

* 5–12 years only.

Admission numbers are a measure of admission need only if there are enough beds. Therefore, before accepting the figures of admissions as an accurate measure of need, we must exclude the possibility that the numbers of available beds have increased and enabled an unsatisfied need to become satisfied. This could have happened if there had been an increase in total beds or if more beds had been freed by a fall in admissions from outside Newcastle. However, there has been no increase in the total, and the proportion occupied by Newcastle children has remained almost constant, being 32% in 1950, 33% in 1955, and 34% in 1957. Moreover, from our day-to-day knowledge of the hospitals we are satisfied that it has always been possible, in all the periods, to find a bed for an acutely ill or injured child. What is more difficult to prove, although we believe it to be true, is that, although diseases and treatments may change, there has been no significant change in the threshold of admission over these years. The prevention of unnecessary admissions rests on the availability of a person of sufficient experience and seniority to decide on each individual admission, and a willingness of the family doctors to cooperate by accepting a hospital decision on the need or otherwise for admission. In very large measure these criteria were fulfilled in Newcastle in 1944 and have remained so since.

We have given evidence that the numbers of children in Newcastle needing admission to hospital each year did not change appreciably from 1950 to 1957. Further evidence is necessary to show whether or not the same number of beds was required to enable these children to be nursed adequately. This problem cannot be approached directly: comparison of the average length of stay in the various years does not suffice, because the average would be affected by availability of beds as well as needs of children. Moreover, when length of stay can vary so widely, from a day to several months, an average figure is of little value. Indirect evidence may be obtained from the nature of the illnesses for which children were admitted.

For this purpose we have used a broad classification of "key diseases" which include the majority of admissions (Spence and Taylor 1954), and the results of this analysis are shown in table VI.

There has been a fall in infective illnesses, especially "fevers", occurring almost entirely between 1944 and 1950; indeed the fall in "fevers" accounts for almost all the total fall in admissions between 1944 and 1950. Between 1944 and 1957 there was a continuous fall in the numbers of children admitted with tuberculosis. (From 1944 to 1950 this fall was largely offset, as regards bed occupation, by the increase of time children with tuberculous meningitis were kept in hospital after the introduction of successful treatment. Since then the number of beds occupied by children with tuberculous meningitis has been almost negligible.) Except for tuberculosis there was little change in the illness pattern of admissions between 1950 and 1957. Although advances in medicine have changed the length of stay in hospital for certain illnesses—

TABLE V—ADMISSION-RATE PER 1000 POPULATION AT RISK

| Age | 1950 | 1955 | 1957 |
|---|---|---|---|
| Under 12 months | 88·6 | 100·6 | 94·2 |
| 1–4 years | 36·8 | 32·0 | 36·3 |
| 5–14 years | 23·3 | 22·8 | 26·2 |

TABLE VI—ADMISSIONS OF "KEY DISEASES" 1943–55

| — | 1943–44 (under 13) | 1950 (under 15) | 1955 (under 15) |
|---|---|---|---|
| *Infective illnesses* | | | |
| "Fevers" | 929 | 180 | 64 |
| Gastroenteritis | 213 | 126 | 86 |
| Abscess, &c. | 250 | 54 | 58 |
| Tuberculous meningitis | 26 | 31 | 5 |
| Other tuberculosis | 111 | 49 | 22 |
| *Respiratory disease* | | | |
| Upper respiratory infection, tonsillitis and otitis | 140 | 240 | 130 |
| Pneumonia, bronchiolitis and bronchitis | 230 | 160 | 160 |
| *Acute abdominal surgery* | | | |
| Pyloric stenosis | 15 | 21 | 19 |
| Intussusception | 13 | 28 | 27 |
| Appendicitis | 42 | 81 | 71 |
| "Abdominal pain"* | 70 | 74 | 75 |
| *Trauma* | | | |
| Bone and joint injury | 56 | 52 | 46 |
| Head injury | 56 | 53 | 75 |
| Burns and scalds | 55 | 33 | 34 |
| Other trauma | 114 | 65 | 66 |
| *Planned surgery* (excluding tonsillectomy) | 154 | 254 | 210 |
| *Miscellaneous* | | | |
| Rheumatism and chorea | 24 | 24 | 16 |
| Nephritis | 11 | 16 | 14 |

* Admitted with provisional diagnosis of abdominal emergency, but found not to require surgery.

sometimes shortening it by speeding cure and sometimes lengthening it by keeping alive children who would otherwise have died quickly—no great change of this kind is likely to have occurred between 1950 and 1957 in those illnesses which have accounted for the great majority of admissions.

A further factor to be considered is " threshold " of discharge, which affects duration of stay just as threshold of admission affects the numbers of admissions. From our knowledge of the hospitals we believe that there has been no appreciable change in the threshold of discharge throughout the period, the policy being always to seek the discharge of a child as early as possible.

From this indirect evidence we conclude that a given number of admissions would require the same number of beds for their care in 1957 as they did in 1950.

### Comment and Conclusions

The numbers of Newcastle children needing admission to hospital (excluding those for removal of tonsils and adenoids and those going to long-stay hospitals) fell somewhat between 1944 and 1950 but have since remained almost constant. We have given evidence that, for the children admitted, the stay in hospital is no shorter than it was, and we therefore conclude that there has been no fall in the bed requirements for children in Newcastle upon Tyne since 1950.

Does this conclusion apply to other parts of the country? We see no reason to suppose that Newcastle differs from other large centres of population in its standards of social conditions or medical care; but away from the main centres conditions are certainly different. Whereas in Newcastle itself 80% of the children in hospital are in children's hospitals or departments, and 92% are under pædiatric supervision, in the Newcastle Region as a whole 66% are in children's hospitals, departments or wards, and only 33% are under pædiatric supervision. We have shown elsewhere (Taylor, Davison, and Spence 1956) that the length of stay of children in hospital rises considerably when they are not nursed in units with pædiatric supervision, and the total number of beds in the country occupied by children might well be reduced if they were concentrated in properly constituted children's units, as has been suggested by *The Lancet* (1958). We may add that the beds saved would largely be beds which do not appear at present as " children's beds " in official statistics, because many of them are in adult wards.

There is much concern—and properly so—that children should be kept out of hospital and nursed at home whenever possible, and for making it easy for parents to visit them when they are admitted. But there are still many occasions when admission to hospital is necessary to effective treatment—and this holds good even though the hospital is some distance from the child's home. The central question, and one which has been ignored in many discussions on the subject, is " What kind of hospital? " (Spence 1946). At present, these vary from teaching children's hospitals, through well-appointed children's departments in general hospitals, fever hospitals, small children's wards with intermittent pædiatric care or no pædiatric supervision at all, to adult wards. We believe that if admission is justified it should be to a unit where experienced pædiatric medical and nursing care can be given—i.e., to a properly constituted children's hospital or department. Ease of visiting does not compensate for long illness, residual disease, or a dead child.

The fact that each year in England and Wales nearly 2000 infants die from acute respiratory disease—many at home—suggests that some who need admission are still not so admitted. That more than 200 children in England and Wales die each year from appendicitis and intussusception, when the mortality from these diseases in experienced hospitals is negligible, again suggests that some are not being treated under optimal conditions.

Some of the steps needed for the rational planning of hospital accommodation for children are clear. First, let the facts be found by inquiries of this kind in other parts of the country. Then let there be a reduction, or indeed an abolition, of beds occupied by children in adult wards and in small, isolated children's wards. But let there be no reduction of beds in established children's hospitals and departments until they have absorbed the children so displaced.

We all look forward to the day when improved preventive measures and more effective home treatment under better social conditions will reduce the number of children needing admission to hospital; but until evidence rather than impression shows that this day has arrived, let us make sure that the beds are available under the right conditions for the children who need them.

### Summary

An investigation has been made into the admission of City of Newcastle children to hospital in the years 1955 and 1957 and the results have been compared with those of a similar investigation during 1943–44 and 1950.

Since 1950 there has been little change in either numbers or character of such admissions, and there is good reason to think that the need for hospital beds for Newcastle children did not fall appreciably between 1950 and 1957.

Before beds in children's hospitals or departments are closed in any part of the country, a similar local investigation should be undertaken.

We are indebted to the medical and lay staffs of the Newcastle upon Tyne hospitals for the facilities afforded to us in finding the facts, and to Prof. S. D. M. Court for suggestions and stimulation.

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". . . We often confuse three criteria in estimating the importance of the great figures in the history of thought. The first is the indispensability of what they wrote or said, regardless of its effect, judged as a stage in the development of our present beliefs. From this point of view, to earn a place in history, a man need only be the first to discover the material or express the idea in question. The second criterion is their effect on other thinkers, and nonthinkers, which, unlike the first, requires publication and recognition (or misinterpretation). The third criterion is the extent of their personal indispensability. To judge this, we must make some estimate of the time that would have elapsed before the same contribution would have been made by others, had the individual under assessment never existed. If we introduce an index of ' lucky fame ' as the ratio of a man's importance on the second criterion to his importance on the third, it seems very likely that Darwin has the highest index of lucky fame in history."—MICHAEL SCRIVEN, *Science*, Aug. 28, 1959, p. 477.

## Public Health

# THE DISINFECTION OF BATH WATER WITH HEXACHLOROPHANE

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DURING a study of cross-infection in surgical wards, we investigated methods of disinfecting baths. We found that addition of hexachlorophane to the bath water before the patient entered the bath made it lethal to staphylococci and some other bacteria, and reduced the number of bacteria left on the surface of the bath.

### METHODS

Hexachlorophane, or di(3 : 5 : 6-trichloro-2-hydroxyphenyl) methane, is almost insoluble in water but soluble in various organic solvents. A stock 10% (w/v) solution was made by dissolving 100 g. hexachlorophane in 400 ml. industrial spirit, and 10 g. sodium hydroxide in about 500 ml. water. The two solutions were mixed and the volume made up to 1 litre with water.

The stock solution was sent to the wards in 1 oz. (28 ml.) bottles. For use, the bath was " drawn ", and one bottle of the solution was poured into the water. The disinfectant was precipitated in floccules which were dispersed by mixing. The patient then took his bath. The volume of bath water varied, but was found to average 30 gallons (136 litres). The final concentration of hexachlorophane in the water was about 1/50,000.

' Tween 80 ' was used to neutralise the hexachlorophane in cultures made from bath water (Bolle and Mirimanoff 1952, Erlandson and Lawrence 1953). This effect was confirmed by inoculating staphylococci on sets of nutrient-agar plates containing varying concentrations of tween 80 and hexachlorophane. (The addition of hexachlorophane was made from alcoholic solutions so as to give a final concentration of 1% of alcohol in all plates.) Tween 80 in a concentration of 0·5% (v/v) allowed staphylococci to grow freely in the presence of hexachlorophane in concentrations up to 1/1000. In the absence of tween 80, growth was prevented by hexachlorophane in a concentration of 1/1,000,000. Tween 80 alone, in a concentration of 3%, did not affect the growth of staphylococci.

### RESULTS

Preliminary experiments showed that *Staphylococcus aureus* and many other bacteria were killed by hexachlorophane in the concentration used in bath water.

Four staphylococci, with different phage-patterns, were tested. 0·02 ml. of the 10% stock solution of hexachlorophane was added to 100 ml. water; after mixing, 1 ml. of the resulting dilution was added to 9 ml. of a saline dilution of an overnight broth culture, which contained about $10^8$ staphylococci per ml. and was held at 37°C. Viable counts were performed immediately and at five-minute intervals by incorporating 0·02 ml. in tween 80 agar and incubating for forty-eight hours. From initial values of about 2000 colonies per plate, the counts fell to zero after five minutes with two of the staphylococci and after ten minutes with the other two. The viable counts in control tubes containing tween 80 as well as hexachlorophane were unchanged after thirty minutes.

In similar experiments gram-negative bacilli were found to vary considerably in sensitivity, but were less sensitive than the staphylococci.

To determine the effect of hexachlorophane on the number of bacteria in bath water several adult volunteers took baths in 30 gallons of water at temperatures between 40°C and 44°C, using plain toilet soap. The standard 1 oz. dose of hexachlorophane solution was added to the water, with mixing, at times which varied in different experiments. 20 ml. samples of the water were collected at intervals in sterile bottles containing 2 ml. of a 20% aqueous solution of tween 80, and after suitable dilution were added to tween 80 agar and incubated for two days. The viable bacterial counts rose from initial values which usually were less than 200 per ml. before the bather entered the water, to several thousands per millilitre within a few minutes of his entry. The addition of hexachlorophane brought about a rapid fall in the count (fig. 1), and moreover subsequently the treated bath water was shown to be bactericidal to five different strains of *Staph. aureus*.

Routine use of hexachlorophane in the baths of a male surgical ward lowered the total bacterial counts considerably (fig. 2). High counts were occasionally seen despite the use of hexachlorophane, when patients with open wounds took baths. Conversely low counts were sometimes obtained from patients who had recently taken several hexachlorophane baths, even when the disinfectant was omitted from subsequent baths. This may explain the low counts seen at the beginning of the second period in fig. 2. These findings may indicate a cumulative effect of the disinfectant on skin bacteria, but require further investigation.

The effect of hexachlorophane on the bacteria remaining on empty baths was investigated by swabbing the baths in three 28-bed male surgical wards, with swabs soaked in a 2% aqueous solution of tween 80.

Some swabs were rubbed over areas of about 3 x 3 in. (7·5 x 7·5 cm.) near the " waterline ", some over similar areas on the bottoms of the baths, and some were stroked nine times along the bottoms of the baths, from end to end. The swabs were inoculated on tween 80 agar. In one of the wards (X) the two baths were cleaned frequently with a scouring-powder but no hexachlorophane was used. The only bath in ward Y was cleaned by the same method, but hexachlorophane was added to the bath water. Hexachlorophane

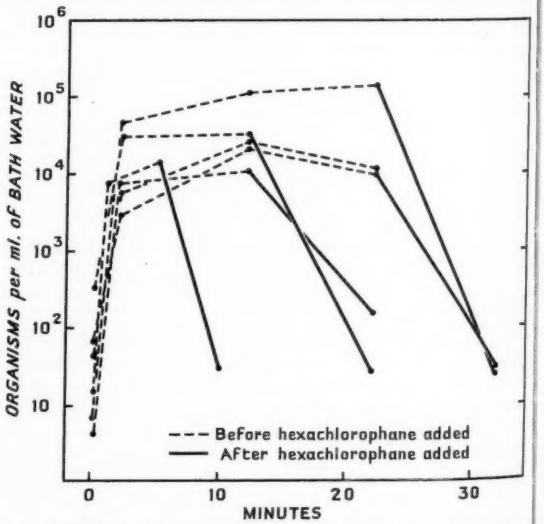


**Fig. 1—Effect of adding hexachlorophane on total bacterial count, at various times after bather entered the water.**

was also used in both baths in ward Z, and as an additional precaution the hypochlorite-detergent mixture described by Boycott (1956) was used to clean the baths.

The swabs from wards Y and Z, where hexachlorophane was used, gave much lower counts and contained fewer staphylococci than the swabs from the control ward X (fig. 3).

Several of the swabs from X yielded heavy growths of *Staph. aureus*. (There were several patients with staphylococcal wound infections in wards X and Y, but few in Z.) The additional use of hypochlorite in ward Z made disappointingly little difference, but this was probably because the hypochlorite was often omitted at busy times, when most of the swabs were taken. Thus a few swabs, taken after a bath was rinsed with water following thorough cleansing with hypochlorite and detergent, were almost sterile.

Hexachlorophane baths have been in daily use in one 28-bed surgical ward for over eighteen months, and in another ward for six months. More than 4000 baths containing hexachlorophane have been taken. Many patients have taken several. The only reports of irritation of the skin and mucous membranes were made by 3 patients who complained of slight irritation of the skin, without visible changes, after taking daily baths for several weeks. Another patient complained of irritation in his unhealed wound. We were unable to determine whether these effects were due to the disinfectant.

The ingredient cost of hexachlorophane solution was less than 3*d*. a bath.

Hexachlorophane has also been added to the water used for "blanket bathing" bedridden patients, in the proportion of $^1/_4$ oz. of the 10% stock solution to about 1 gallon of water.

## DISCUSSION

That contaminated baths may be important agents in the transfer of staphylococci from patient to patient has been pointed out by Colbeck et al. (1956) and others. The danger is greater if the same bath-tubs are used by patients before and after operation—an undesirable practice which may be hard to prevent in oldfashioned wards with few bathrooms and no shower-baths.

Several methods of disinfecting baths have been described. We have found the method of Boycott (1956) satisfactory, provided the bath is thoroughly rinsed with the hypochlorite-detergent mixture after use by every patient. But this has been difficult to ensure in busy wards where the one or two baths are in frequent demand. Some ambulant patients bath unattended, and neither they nor the ward domestic staff easily remember to disfect the bath after use. On the other hand it has been easy to establish the routine practice of adding hexachlorophane to every bath before the patient enters the water. *Staph. aureus* is among the most sensitive of organisms to hexachlorophane. In the concentration we have used, hexachlorophane can be relied upon to kill most staphylococci and many other bacteria. But some bacteria, including gram-negative bacilli, are relatively insensitive. We prefer, therefore, to combine two precautions, using hexachlorophane in the bath water and a disinfectant rinse by Boycott's method when the bath has been emptied.

Hexachlorophane in a higher concentration might give better results and a detergent might be incorporated in

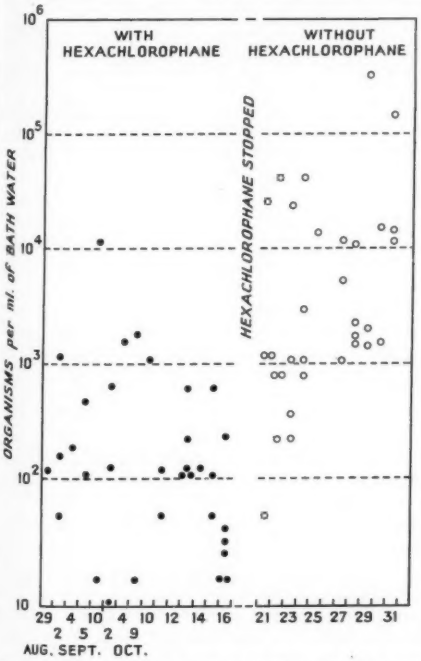


**Fig. 2—Total bacterial count in bath water with and without hexachlorophane.**

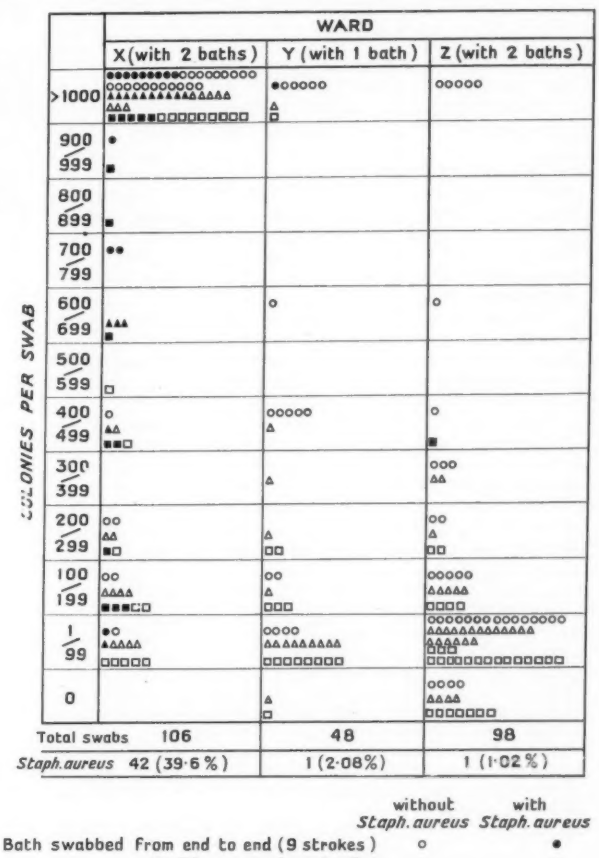


**Fig. 3—Effect of disinfecting baths (see text).**

the stock solution to facilitate dispersion in the bath water. In preliminary tests, a 10% water-miscible preparation of hexachlorophane (' Ster-Zac ' bath concentrate) was found to disperse rapidly in water and was at least as active against staphylococci as our stock preparation.

Besides disinfecting the baths, hexachlorophane in the water might reduce the numbers of staphylococci on areas of the patient's skin which are sometimes colonised by these organisms (Hare and Ridley 1958). In a preliminary study we found that a single hexachlorophane bath had no demonstrable effect on perineal carriage of *Staph. aureus;* but the effect of repeated baths would be worth investigating.

SUMMARY

The addition of hexachlorophane to bath water was shown to destroy staphylococci and many other bacteria. It may thus help to control cross-infection.

We thank Mr. G. H. Darling and Mr. E. George for their help with the preparation of hexachlorophane solution, and Mr. H. Critchley for collecting samples of bath water. We also thank Messrs. Hough, Hoseason & Co. for a supply of ' Ster-Zac ' hexachlorophane bath concentrate.

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## Breast-feeding

IN his annual report for 1958, Prof. A. B. Semple, medical officer of health for Liverpool, describes a lactation survey, undertaken between January and September, in which health visitors visited 7272 mothers when the baby was about 6 weeks old.

At this time, of infants born in hospital 25·1%, and of those born at home 24·7%, were wholly breast-fed. Of 3963 mothers with normal breast conditions 2058 (51·9%) sought artificial aid to stop lactation. Of these, 523 (25·4%) received tablets from the hospital, 1446 (70·3%) received tablets from the general practitioner, and 89 (4·3%) received tablets from a pharmacist.

There was no notable difference between hospital and home deliveries in respect of the incidence of breast abscess, the figures being 2·5% and 2·6% respectively. The incidence of sepsis in infants born in hospital was 10·6%, and in infants born at home 10·1%.

Breast abscess and sepsis in the infant were closely correlated. Of the infants of women delivered in hospital who had breast abscesses, 23·4% had some sign of sepsis; the corresponding figure for domiciliary deliveries was 21·7%. In the infants of mothers with normal breast conditions, the incidence of sepsis was 9·7% where the delivery had taken place in hospital and 9·2% where it had taken place at home.

## Vaccination Against Poliomyelitis

The campaign for poliomyelitis vaccination of young people has been intensified in two of the London County Council's health divisions in north London.

Copies of a letter by Dr. J. A. Scott, the L.C.C.'s medical officer of health, have been sent to firms, coffee bars, dance halls, hairdressers, gramophone-record shops, and others, asking for their help. In his letter Dr. Scott points out that quite three-quarters of Londoners aged 15–26 have not yet sought immunisation.

Posters, window-stickers, car-stickers, leaflets, and wage-packet slips have been distributed; and a mobile clinic is operating near factories and offices.

## Arsenic

Contamination of drinking-water by an arsenical spray intended for potato crops is suspected to be the cause of the death of a woman of 38 and the illness of her husband and three children.[1] Two other people sharing the same water-supply at a farmhouse in Bringsty, Herefordshire, were also taken mildly ill. It is possible that during mixing of water and spray powder something like a blow-back caused contamination of water in the storage tank.

# Dialogues of Today

## CRIME AND PUNISHMENT

SOCRATES: You said the other day, Apollodorus, that if a criminal, because of his mental disorder, did not know what he was doing, or that what he was doing was wrong, he would not be punished for his offence, and that lesser degrees of mental illness might lead to the conclusion that the offender's responsibility for his act was diminished, in which case his punishment would be less than it would otherwise have been.

APOLLODORUS: That is so, Socrates.

SOCRATES: For what reason do you think punishment should be given?

APOLLODORUS: There seem to me to be three main reasons for punishment—to deter others, to deter the criminal from repeating the offence, and if possible to reform him.

SOCRATES: Which of these objects do you think the most important?

APOLLODORUS: The first two, Socrates; for, while it is desirable to reform the criminal if possible, that seems to me of less importance than deterring him from committing further offences, and others from following his example.

SOCRATES: Do you think, then, that an insane person ought not to be punished—because punishment would be unlikely to have a deterrent effect on him, or reform him, and could hardly deter normal people, who would not imagine themselves as likely to commit the same kind of crimes as an insane person?

APOLLODORUS: Yes.

SOCRATES: But you say that a person who has diminished responsibility for the offence should receive a lesser sentence. Does that mean that, being irresponsible, he will be more easily deterred than a normal person, or that responsible people will be more easily deterred by a lesser sentence inflicted on an irresponsible one? Or is it that, being irresponsible, he can be reformed by a shorter period of detention?

APOLLODORUS: None of those can be the reason, Socrates; but surely it would not be just that a partially responsible criminal should receive the same punishment as a fully responsible one.

SOCRATES: It seems to me, Apollodorus, that you have now introduced a principle which you have not mentioned before. Do you hold that, as well as being a deterrent and a reforming influence, a punishment may be just or unjust? And is its justice something different from these other characteristics, or is it merely another name for one or both of them?

APOLLODORUS: I think justice is a principle different from deterrence and reform; for it is possible that an unjust sentence might act as a greater deterrent than a just one, yet if it is unjust it ought not to be inflicted. And if justice requires that a man should be executed it is hardly compatible with his reform.

SOCRATES: Would you then give justice priority over these other considerations?

APOLLODORUS: Certainly.

SOCRATES: What, then, is a just punishment?

APOLLODORUS: I do not think you can define justice in rational terms, Socrates, for it is a matter of feeling. All right-thinking men feel that it is right that crimes should be punished, and the general validity of this is shown by the fact that they would accept it in relation to themselves, if they chanced to be the criminal.

1. *Times*, Sept. 14.

SOCRATES: If justice is a matter of feeling, should you not speak of right-feeling rather than right-thinking men? And who is to decide which feelings about justice are right? One man feels capital punishment to be just, another does not. One man would punish private homosexual offences severely, another would have the law disregard them. How do you decide between them?

ANALYTICUS: Apollodorus is more right than I think he realises, Socrates, and you could not have chosen two better illustrations. If men who are equally wise and conscientious differ on such questions we should suspect that their differences are not rational. Psychology shows that we learn to feel guilt for unconscious reasons. How we deal with our own sense of guilt will determine our attitude to the guilt of others. Abstract justice is a rationalisation of our sense of guilt modified of course by social factors. But it would be possible in theory to devise a way of dealing with offenders which would fulfil the needs of society without arousing any of the strong emotions of which judges' homilies, and the Sunday newspapers, are only two different expressions. We are a long way from that yet, but perhaps not so far as you might think. I suspect that the deterrence theory of punishment is another rationalisation, which will not stand up to statistical evidence. Anyway justice and deterrence between them seem to be leading to more crime and fuller prisons. If we still believe in them in the face of that evidence, it suggests that our belief is not entirely a rational one.

## Medicine and the Law

### Indecency with Children

THERE is at present a gap in the law relating to acts of indecency with children. Such acts can often be punished under the heading of indecent assault, but there are cases of indecent behaviour which do not involve anything which can properly be called an assault—e.g., where a person successfully invites a child to handle him indecently.

To close this gap in the law, the new Criminal Law Revision Committee [1] recommend legislation to penalise "Any person who commits an act of gross indecency with or towards a child under the age of fourteen, or incites a child under that age to such an act with him or another".

The committee regard the first limb ("commits an act of gross indecency with or towards a child under the age of fourteen") of this suggested provision as the more important; it would cover successful invitations of the kind already mentioned and also, they think, most of the other kinds of conduct likely to occur. The second limb ("incites a child under that age to such an act with him or another") would cover cases where the accused's conduct does not result in an offence by anyone under the first limb (for instance, because the incitement is unsuccessful, or because the resulting act of indecency is between two innocent children incited to do it for the gratification of the accused).

The suggested offence would apply to persons of either sex who have reached the age of criminal responsibility.

It is proposed that the maximum penalties should be six months' imprisonment and/or a fine of £100 on summary conviction; or two years' imprisonment on conviction on indictment.

The committee's proposals cannot be implemented without legislation which cannot now be introduced until after the general election.

1. Criminal Law Revision Committee; First Report. Cmnd. 835. H.M. Stationery Office. 6*d*.

## In England Now

*A Running Commentary by Peripatetic Correspondents*

BUYING gas is one of the joys of American motoring. There is an indefinable thrill about pulling in at the gas station and giving the peremptory "Fillerrup!" (preferably spoken out of the corner of the mouth). The novice need not be disconcerted if the attendant leaves the pump to churn by itself for a full five minutes while he busies himself with tyre pressures, battery, radiator water, and wind shield. Some of those acromegalic saloons hold over twenty gallons, which, even so, will only come to six bucks (about forty shillings sterling). As a matter of fact, by going a little out of one's way, one can often save a few shillings, thanks to the gas wars. These arise because rival companies get it into their heads from time to time to see which can sell the cheapest petrol, which then gets cheaper and cheaper down the line until someone is actually selling the stuff at a loss. Of course nobody is prepared to keep this up for long, and a truce is usually called at this juncture. Meanwhile, delighted motorists rush back and forth, filling up anything they can lay their hands on. The arrangement is admirable for everyone, with the possible exception of the proprietor of the garage with the king-size discount. New Englanders, proud of their Scots blood, enter into the spirit of the gas wars with exceptional enthusiasm and will often go fifty miles out of their way to find the cheapest gas around town. Competition amongst garages is so keen that all kinds of inducements have to be thought up by imaginative proprietors. Some offer a 30-second car-wash or a free change of muffler—i.e., a new silencer (you pay double for the silencer, but the screwing on and off is free). Slot-machines are popular bait, and most self-respecting garages have a drive-in 'Coca-Cola' automat from which you can get your iced coke without having to get out of the car. For some extraordinary reason, slot-machines for nail-clippers are also great favourites. An ingenious gimmick of one garage is to give away toll tickets for the bridge five miles up the highway, saving the casual motorist 25 cents, though the owner, who bought them by the month, paid only a fraction of this.

All this contrasts to the ill-treatment heaped on a submissive public by the British garage. It takes courage to ask to have one's windows wiped, and you have to be a longstanding customer of special merit before you are let in on the secret that the air-pressure gauge is not, and never has been, out of order. Particularly despicable is the cunning psychology behind the arrangement of the pumps, so that Super-Extra-Zing-Plus-Go is served by several pumps while the ordinary common-or-garden petrol (on which, as it happens, my car exceeds all expectations) has only one pump. Even if one has the will-power to face the long wait caused by this arrangement, one's temerity is likely to succumb to the second crafty ruse, whereby the one and only pump for ordinary petrol is placed at the approach of a narrow entrance so that a formidable traffic jam is apt to arise with startling and embarrassing rapidity. Then, over a cacophony of hooting, the pump attendant, with an expressive gesture of the thumb and in a voice tinged with the exactly right overtones of resignation, deprecation, and scorn, announces for all to hear: "Yer can't move till 'e's 'ad 'is *cheap*!"

* * *

Last year while I was peripatetic in England I spent considerable time remedying a condition, aggravated by dusty years in the tropics, designated *Aworthingtonæmia* by a medical colleague. The therapy evoked pleasant meditations tinged with melancholy; I began to think of retirement, of comfortable gradual ageing, like fine old ale in a cask, with just enough work to keep the spirits from flagging. And I thought to myself, why not keep a pub? A quiet country pub; mellow brick and ivy without, well-rubbed tables and shining brass within. And a cozy ingle where old cronies could forgather, hot from Harley Street or chilled by academic rigors. My wife, bless her, said yes.

But first we must have a name. No use a pub without a name, even if it's still a hypothetical pub. None of the common ones, enticing though they be—*The Coach and Horses, The George and Dragon, The Star and Garter. The Ship*? No, we had enough of those. *The Cat and Kittens*? More my style, but a bit Beatrix Potter for an old boy. *Ye Olde Plough Horse*? Too near the mark. But there's a thought—if *The Plough and Harrow* is acceptable, why not *The Scalpel and Scissors*? My wife thought not. Try history then, *The Smellie Tavern, The Semmelweis Saloon, The DeLee Dive.* We seemed to be drifting away from our simple ivy-clad publet.

We haven't talked about it since. But I still think about it, sometimes, when the tumult of the quiet tropic night keeps me from sleep. *The Locked Twins; The Grande Multipara; The Call at Midnight; Man-Midwife's Rest.*

* * *

All doctors, as part of their training, should spend a month as a patient in hospital. Every reader who has been a patient will have suggestions for such a clinical novitiate. I am particularly fond of the trial by " laughter in the next room ". After a murmured conference at the bedside, registrar and house-physician disappear into the office whence gales of unseemly mirth at once emerge. For those who come through this and other trials a further fortnight as an anxious relation would be a valuable experience.

I submit that a programme of this kind might well produce doctors more humble and humane than those commonly met with at least during the early postgraduate years. As a wife and mother, it also occurs to me that a similar suggestion might be offered to the pupil midwife; but I can well see that there might be technical difficulties.

* * *

Now that the holiday season is here again, we have noticed a phenomenon which, although it seems to be common, has not (we believe) been mentioned in the literature. We refer to the fact that one's patients always appear much better when one returns after a couple of weeks away.

This inescapable observation is a little unwelcome to those who believe in the doctor-patient relationship as a therapeutic factor, but with disinterested zeal we have planned a controlled study. Having recorded the initial improvement, we shall note our patients' progress over the first two weeks after our return. Should they relapse, it will clearly be in their best interests for us to go away again. This time we shall stay away for three weeks, so as to determine the optimum period of absence.

We are prepared to continue this experiment, perhaps with varying lengths of absence, until a firm conclusion is reached; and we are now only waiting for the management committee's approval to get started.

* * *

Adders are apparently not the most awkward intruders a water closet can hold. An elderly lady on safari writes with enviable detachment from a camp in Central Africa:

" There are a few round huts with some simple furniture and beds and a wee kitchen and some earth closets. The closets are full of bats which flutter *into* the hole in the seat when one goes in and disturbs them. This upsets some people's nerves though I do not mind them. But it does give you a funny feeling sitting over alarmed bats."

* * *

*Out of the Garden*

My plot's
A row of pots;
The ground I till
A London window-sill.
I keep plants in fine fettle
By watering them from a kettle.
A gas fire's pungent fumes
Improve my hardy blooms.
Gardening in an attic
May not be dramatic,
But this I know;
Things grow.

# Letters to the Editor

## BEDS FOR CONFINEMENT

SIR,—It is clear, as Dr. Abercrombie has said (Sept. 19), that a mounting obstetric demand on the Emergency Bed Service calls for immediate action. Further consultations between all those engaged in the maternity services have already been arranged and will take place during the next few weeks. There are signs too that measures which were suggested at earlier meetings are now beginning to take effect, and there is some reason to think that the zenith may now have been passed.

The question of a more rational allocation of hospital maternity beds in London has been the subject of a number of meetings in the past few years between the Local Health Authority, the four Regional Hospital Boards, boards of governors of teaching hospitals, and the Local Medical Committee. The provision of maternity beds—over 80% of all confinements—is already much higher than in many other parts of the country. No difficulty is experienced in admitting for hospital confinement the mother who needs a bed on obstetric or medical grounds. It is the expectant mother who requires a bed on social grounds who may not be able to book a hospital bed. The problem is complicated by a large turnover of population and by the immigration of people of other races, many of whom make no arrangements for confinement until late in pregnancy. Furthermore, the illegitimacy-rate is more than double the national figure.

In local-health-authority clinics doctors, health visitors, and midwives invariably contact several hospitals—often as many as 10—before they are forced to refer an expectant mother who requires a bed on social grounds to her family doctor to get her into a maternity hospital under the Emergency Bed Service procedure. If the general practitioner is unable to undertake this the domiciliary midwife goes out to take the necessary action. Moreover, in the North-West area of the County where the pressure has been greatest, the local health authority, although it has no control over admissions to hospital beds, has set up a bed bureau. Its function is to contact maternity hospitals to seek admission for mothers who require a hospital bed, at the time of their first attendance at the antenatal clinic. It would be unfortunate if the blame for the present state of affairs were quite wrongly to be attributed to any failure on the part of clinic doctors or midwives to take all possible steps on behalf of these mothers.

Public Health Department,
County Hall, London, S.W.1.

J. A. SCOTT
Medical Officer of Health.

SIR,—Your annotation of Sept. 19, which states that " many mothers could and should be sent home by ambulance 24–28 hours after delivery ", and presumably this includes babies too, must cause some concern and despondency among many pædiatricians who are devoting much energy to the problems of the newborn infant in an attempt to reduce neonatal mortality, and minimise the effects of morbidity with its occasional long-term consequences for the child.

The hard core of the problem lies in the first four days of life. During this time the newborn infant is an extremely unstable organism, undergoing rapid changes to adapt to the extrauterine environment, and the effects

of birth stress and signs of congenital malformation or disease may show themselves at any time during this period of life. Whilst intelligent anticipation of some problems may be made from careful assessment of the maternal history and labour record, sufficient attention is often not paid to small details, and unexpected difficulties occur far too frequently for them to be dismissed as a negligible incidence of all births. For example, it is still far too rarely recognised that the rapid easy birth in a multiparous woman, when the midwife arrives only just in time for the delivery, usually termed a " normal " case, may be fraught with danger for the infant who develops cerebral or meningeal œdema subsequently.

Unfortunately for the planners, these neonatal problems are often not recognisable during the first 24–28 hours after delivery, and examination by the most experienced pædiatrician might fail to detect abnormality at that age, for signs so often develop insidiously even as late as the third day. If we are serious in our desire to reduce neonatal mortality to the lower rates prevailing in some other countries, then each case that " goes wrong " is of importance. The best chance for the child seems to be in the good maternity hospital where careful and continuous nursing and medical observation and records are made during this critical first 3–4 days. Under these conditions slight departures from normal behaviour in the child are quickly detected and can be acted on before the child's condition deteriorates to a serious state.

I would therefore put in the strongest plea that as many mothers as possible should be admitted for delivery, but that mother and baby should remain in for a minimum of four days. This could surely be achieved by adopting the practice of North America that the length of stay in hospital for booked cases is normally 5–7 days. There are no great disadvantages to the infant in return home at that stage provided adequate supervision of infant feeding, which includes accurate weighing of the baby if necessary, can be carried out by a domiciliary nursing service. Nowadays the mother, in normal cases, is already ambulant by that stage and does not require the full hospital care service.

I am well aware that some of my colleagues may raise the bogy of risk of infection. This of course cannot be dismissed too lightly, but only a brief glance at recent statistics is sufficient to show the small part that this now plays in neonatal mortality as compared with the much greater hazards already indicated. In my experience the most lethal neonatal infections in recent years have arisen in domiciliary nursed babies where they remained unsuspected until too late. The more rapid turnover of cases that is implied when stay in hospital is shortened does however necessitate the raising of standards of newborn care, both medical and nursing, in all maternity hospitals to those prevailing in the hospitals where at present the lowest mortality and morbidity rates are obtained.

One can only agree with you that in order to achieve the pattern of maternity care that is not only the minimum essential on medical grounds but is also desired by the community, the time is long overdue when the pattern of training for pupil midwives should be radically overhauled, so that it no longer acts as the major stumbling block whenever adaptation of the maternity services to present needs is considered.

Bristol. BERYL D. CORNER.

## THE ROLE OF THE PÆDIATRICIAN IN MENTAL ILLNESS

SIR,—We would endorse the main thesis of Dr. Tizard and his colleagues (Aug. 29) that pædiatricians should be better trained in child psychiatry, but we are disappointed to learn that, in their view, we are practising pædiatrics so badly. Ours is a general pædiatric practice, similar to many thousands of others on this continent, and our work is probably not so very different from that of a provincial pædiatrician in Britain. 75% of our time is spent in advising mothers on how to feed or how not to feed their babies, how to cope with minor feeding and behaviour disorders, and we examine hundreds of children each year to reassure their parents that they are in good mental and physical health. We thought that we were doing a reasonably good job, but how wrong we find we are. We do not think it matters very much what kind of milk a baby is given (except that breast milk is probably best), but unboiled milk from the local farm is probably not very good. We do think that vitamins prevent deficiency diseases and that if a purely milk diet is continued too long iron-deficiency anæmia will result. We advise mothers accordingly, but this is wrong we are told. We should let them find out for themselves.

We are not very successful in treating enuresis, but we try hard and we wonder if child psychiatrists do really so much better than us. In the older enuretic we have been in the habit of investigating the renal tract to exclude the occasional organic disorder which might be treated. It now seems that we should wait and " be prepared to look foolish " when time shows up any such disease by the occurrence of uræmia or hypertension. We think we are a little better at treating fæcal incontinence by suggesting the avoidance of constipation and overflow by intelligent toilet training. This we think is common sense, and common sense came before Freud. Common sense was certainly an attribute of our Olympian predecessors such as Osler, Still, Parsons, and Spence.

> " Are we so much wiser grown
> That we cannot in our day
> Make their words our own."—Whittier.

But Dr. Tizard would have us believe that the days of the Olympian physician are past.

In short what is apparently needed in this city of half a million people is not 15 pædiatricians but 150 (or 1500) child psychiatrists, each of whom can afford to spend an hour or two listening to a mother talking about her child's thumbsucking. We fear that as busy pædiatricians we can afford only 10 minutes to tell her that it doesn't matter.

M. MCLANDRESS
J. C. HAWORTH
J. N. BRIGGS
K. C. FINKEL.

Winnipeg Clinic,
Winnipeg, Manitoba.

## MARJOLIN'S ULCER

SIR,—I wonder whether any of your readers can explain why a carcinoma occurring in a venous ulcer is now often called Marjolin's ulcer?

This eponym is in current use in many of the teaching hospitals both in this country and in the U.S.A. In response to a query of mine, a surgical registrar at a London teaching hospital took a Gallup poll on " What is a Marjolin's ulcer? " 80% voted for carcinoma secondary to a varicose ulcer.

My collaborator, Mr. W. J. Bishop, Editor of *Medical History*, can find no reference to varicose ulcer in

Marjolin's works. The best authorities define Marjolin's ulcer as a carcinoma occurring in scar tissue, particularly scar tissue following burns.

Sholden, near Deal, Kent. HAMILTON BAILEY.

## ACUTE ANHIDROTIC HEAT EXHAUSTION

SIR,—May I report a case of "acute anhidrotic heat exhaustion" which occurred in London this year?

Mrs. T., aged 45, underwent bilateral oophorectomy and adrenalectomy for carcinomatosis on May 6, 1959. In the middle of the afternoon of May 8 she suddenly became drowsy and confused, in spite of adequate steroid replacement. Her oral temperature was 101°F, and her skin was flushed, hot, and bone dry. She recovered within 12 hours. May 8 had been a sunny and windless day, and the ward was hot and rather humid.

The patient weathered the summer heatwave without discomfort, sweating normally. On September 8, a very warm day, she was readmitted to another department with severe neck pain due to bony deposits. That evening she had a temperature of 104°F, and she was noticed to be sweating very little. She had recovered by the next day.

Testing with intracutaneous methacholine on May 10 had suggested a deficient sweat-gland response; but this was not borne out by her condition during the summer. The other complication in this lady is that intracranial deposits have been suspected, and a hypothalamic lesion cannot therefore be ruled out.

The Middlesex Hospital, London, W.1. P. MESTITZ.

SIR,—I was surprised to learn from Dr. Bannister's paper (Sept. 12) how recently this condition has been described. It would seem to have been familiar to Anglo-Indians of an earlier generation, however, because it is clearly indicated by Kipling in his short story At the End of the Passage (*Life's Handicap*, 1891).

The scene is set at night with the thermometer reading 104° and the doctor says: "'It occurs to me that unless I drink something I shall go out before my time. I've stopping sweating, and I wear a seventeen-inch collar.' He brewed himself scalding hot tea, which is an excellent remedy against heat-apoplexy if you take three or four cups of it in time."

Solihull. W. BRIAN GOUGH.

## REACTIONS AFTER INTRAVENOUS IRON-DEXTRAN

SIR,—During investigations of plasma volume using the intravenous injection of iron-dextran complex ('Imferon'), as described by MacKenzie and Tindle,[1] we have recently encountered two cases of severe anaphylaxis. In both cases an intravenous injection of imferon had been given 2 weeks previously without any ill effect.

CASE 1.—A man, aged 65 years, suffering from polycythæmia vera was given 1 ml. imferon intravenously to estimate plasma volume. There was no ill effect of any kind. 14 days later a further intravenous injection of 1 ml. was slowly given: after 5 minutes the patient became extremely suffused and had a very full bounding pulse: this state lasted for about 4 minutes and was followed by collapse, pallor, sweating, a rapid, feeble pulse, and severe pain in the loins. He was given subcutaneous adrenaline and intravenous hydrocortisone and gradually recovered.

CASE 2.—A male volunteer aged 71 years who had had a myocardial infarction 3 days previously was given 1 ml. imferon intravenously without any ill effect. 13 days later during the very slow administration of a further 1 ml. he became very suffused after only 0·2 ml. had been given. The injection was immediately stopped and the subsequent development of collapse, sweating, and severe pain in the loins was treated with adrenaline and intravenous hydrocortisone. Complete recovery took place after a few hours and there was no subsequent rise in serum transaminases (S.G.O.T. and S.G.P.T.). Before the second injection of iron-dextran the serum-iron level was 130 μg. per 100 ml. and the total iron-binding capacity was 310 μg. per 100 ml.

We consider that these two reactions are truly anaphylactic and not "toxic" on the following grounds:

(*a*) The nature of the reactions and the time relationship of the two injections.

(*b*) The small amount of iron given, particularly in case 2.

(*c*) The evidence that in case 2 the serum was not saturated with iron.

(*d*) The intravenous injection of 1 ml. iron-dextran without reaction a fortnight previously.

Several other elderly patients have been given, without reaction, two intravenous injections of iron-dextran at an interval of 7 to 8 days and repeated therapeutic doses of intravenous iron-dextran have been given safely to many younger subjects.

The development of a suitable skin test may provide a safeguard but until then it would seem prudent to restrict the use of intravenous iron-dextran to subjects who have had no iron-dextran in the past, whether intravenously or intramuscularly. In such subjects the use of intravenous iron-dextran should be limited to within a period of 7 or 8 days.

General Hospital, Sunderland. A. MACKENZIE
IAN R. LAWSON.

1. MacKenzie, A., Tindle, J. *Lancet*, 1959, i, 333.

## HYDROFLUMETHIAZIDE

SIR,—The three papers in your issue of Sept. 12 describe the properties of hydroflumethiazide and show that it is a diuretic of considerable potency with properties and dosage range very similar to those of dihydrochlorothiazide.

At Whittington Hospital Dr. H. E. S. Pearson and I have used hydroflumethiazide for over six months in the treatment of œdema due to congestive cardiac failure with considerable success.

It soon became important to ascertain whether hydroflumethiazide shares with chlorothiazide the property of enhancing the hypotensive action of ganglion-blocking drugs. This may be on occasion a useful property but it is not without its dangers to the unaware, since interrupted treatment with this group of oral diuretics given to patients who are also under treatment with ganglion-blocking agents for hypertensive heart-disease may have dire consequences.

For some time I have felt that the routine addition of chlorothiazide to ganglion-blocking agents is not justified, as potassium deficiency must be guarded against with the addition of potassium salts, and estimations of the serum-electrolytes are prudent at least at monthly intervals, thus adding to the complexities of the regime.

At the time when the first experiments were performed the tertiary amines, mecamylamine and pempidine tartrate, were in common use. In eight acute experiments on inpatients, hydroflumethiazide in dose of 100 mg. in the morning proved to have, in five cases, a similar but not so powerful enhancing action on mecamylamine and pempidine as 1 g. of chlorothiazide. In the other three cases little enhancing action was noted with both drugs. In twelve more chronic experiments (the patients being followed up at fortnightly intervals in the hypertensive clinic), hydroflumethiazide in daily dose of 50 mg. in the morning appeared, when substituted for chlorothiazide 0·5 g., to have a similar but slightly less powerful enhancing action.

When mecamylamine and pempidine are the ganglion-

blocking agents used in conjunction with chlorothiazide, two different mechanisms come into play. In the first place hypovolæmia is produced by the diuretic and, as Dollery, Harington, and Kaufman [1] have shown, it is in the main the hypovolæmia which enhances the hypotensive action of all ganglion-blocking drugs. Dunstan et al.,[2] who reported similar findings, observed that hypovolæmia leads to a compensatory neurogenic vasoconstriction—a situation in which arteriolar tone is more exposed to the action of ganglioplegic drugs. On the other hand Harington, Kincaid-Smith, and Milne [3 4] showed that the shift of urinary pH to the alkaline side after chlorothiazide, retards the urinary excretion of mecamylamine and pempidine and thus enhances their action. It is not surprising that hydroflumethiazide, which has a smaller carbonic anhydrase inhibitaction than chlorothiazide and does not change the pH of the urine, should have a similar but smaller enhancing effect on these ganglion-blocking drugs than chlorothiazide.

When bretylium tosylate (' Darenthin ') became available for clinical trials, it was thought useful to determine whether hydroflumethiazide has an enhancing hypotensive effect on this drug. Rosenheim et al. in one case [5] and in others (personal communication) have already shown that chlorothiazide in dose of 1 g. has an enhancing effect on bretylium tosylate.

Dollery et al.[1] reported postural hypotension following chlorothiazide alone in a patient who had previously sustained a thoracolumbar sympathectomy—a situation very similar to that obtained after administration of bretylium tosylate. I can now confirm in eight cases that hydroflumethiazide potentiates the hypotensive action of bretylium tosylate similarly to chlorothiazide when given in equivalent doses of 1 : 10.

The prospect of bretylium tosylate and hydroflumethiazide will shortly become drugs of moderately wide application seems a sufficient reason to request so much of your valuable space to make known these observations at an early date.

My thanks are due to Dr. H. E. S. Pearson for permission to mention his findings on the diuretic action of hydroflumethiazide in congestive cardiac failure, to Dr. T. Binns, of Glaxo Laboratories, for generous supplies of hydroflumethiazide (' Naclex '), and to Dr. P. O. Jones, of the Wellcome Foundation, for supplies of bretylium tosylate (' Darenthin ').

Whittington Hospital,
London, N.19. E. MONTUSCHI.

## A COLLEGE OF PATHOLOGISTS

SIR,—Before any more well-intentioned pathologists force upon us a new college no-one wants, it might be explained that we psychiatrists have, in effect, had our College (and a Royal one at that) for well over a hundred years. Although the premises in Chandos Street lack something of the grandeur which regal recognition deserves, the Royal Medico-Psychological Association surely meets most of the needs of psychiatrists for congregation, education, and representation—though the latter point is perhaps open to debate. It has no academic barrier, which is surely right (there are too many diplomas already); it is as easy to join as the Royal Society of Medicine and a good deal cheaper. The Association also has its own periodical (the *Journal of Mental Science*) and four active sections—mental deficiency, research and clinical, psychotherapeutic and social, and child psychiatry. Learned meetings are quite frequent and very well attended, yet many of the luminaries are proud to take an active interest in the affairs of the Royal College of Physicians. One never has the sense of the R.M.P.A. being a splinter group, nor of divided loyalties. Dr. J. A. U. Morgan was surely joking when he said (Sept. 19) that our claims to autonomy were " nearly as good " as theirs: pathology has always been far closer, surely, to internal medicine both in science and administration and pathologists numerically fewer. But if pathologists want their own organisation they could do worse than consider a Medico-Pathological Association along the lines of ours.

London, S.E.5. RICHARD FOX.

1. Dollery, C. T., Harington, M., Kaufman, G. *Lancet*, 1959, i, 1215.
2. Dunstan, H. P., Cumming, G. R., Corcoran, A. C., Page, I. H. *Circulation*, 45, 360.
3. Harington, M., Kincaid-Smith, P. *Lancet*, 1958, i, 403.
4. Harington, M., Milne, M. D. *ibid.* 1958, ii, 6.
5. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *ibid.* July 11, 1959, p. 17.

## PERCEPTUAL ISOLATION USING A SILENT ROOM

SIR,—The interesting findings of Dr. Smith and Mr. Lewty (Sept. 12) raise a number of questions relevant to the study of hypnosis and the possible extended use of such a silent room as a therapeutic aid.

Working daily on research in hypnosis, or with hypnosis as a research tool, I have come to regard the hypnotic trance as resulting, in part at least, from a limitation of perceptual experience through a process of sensory " takeover " by the hypnotist. This is achieved by suggestion, and what the hypnotist takes over are in effect the subject's channels of communication with the outside world, or his contacts with the available sources of information in his environment—to use current terminology. In most techniques of hypnotic induction this is done through the sense of hearing. When, for example, the hypnotist implies in his induction monologue that the smarting of the eyes consequent upon an unblinking stare is due to his suggestions, he takes over responsibility for whatever Lockean " ideas " on corneal and conjunctival experience are then being received at the perceptual level. The hypnotist thus goes on record as having caused the smarting by his suggestions. Similarly, the inevitable fatigue of the levatores palpebrarum superiores when the upper eyelids are hyperelevated for periods up to one minute or more is easily accepted as being the result of the hypnotist's timeworn suggestion: " Your eyelids will get heavy and will want to close . . ." In the same way, during deepening of the trance, proprioceptive impulses are taken over when slight and unconscious movements of the fingers are " fed back " by suggestion as being the results of previous suggestions.

By means of such techniques practised on suitable subjects, the information capacity of the total sensory mechanism would seem to be reduced and a large part of the perceptual experience of the subject can eventually become dependent upon the hypnotist's suggestions via the 8th cranial nerve. Something akin to " unconsciousness " then prevails—in many cases complete, with loss of hearing for anything but the voice of the hypnotist, loss of time-sense, and total amnesia for all events during the trance, plus some seconds of retrograde amnesia covering the period of induction.

By means of the silent room, Dr. Smith and Mr. Lewty seem to perform a somewhat similar operation—in their case by takeover of the sources of information, rather than the channels of communication. If as a result of these experiments (and those at McGill and Princeton) actual unconsciousness was not reached, it may very well be that total isolation has not yet been achieved, as would be demanded by the quoted theories of Grey Walter and interpretations of clinical evidence by Sir Russell Brain.

It would, however, be interesting to determine how easily hypnosis can be induced under such conditions of perceptual isolation. From these findings it seems possible, if nothing more, that a silent room might prove to be a simple means of hypnotising the unhypnotisable 10% of the population, or making light-trance and medium-trance subjects, said to be each 35% of the population, into deep-trance subjects who normally constitute only 20%—or even into " very deep trance " subjects capable of eidetic imagery and regression, who apparently make up less than 2%. The hope is that

deep-trance hypnosis might then be made available to all, for psychotherapy, for the relief of psychosomatic conditions by direct suggestion, and even for the production of surgical anæsthesia or the control of pain in terminal carcinomatosis, instead of being limited as at present to 1 patient in 5, or less.

Psychiatric Department,
West London Hospital,
London, W.6. STEPHEN BLACK.

## THE NATURE OF EXPERIENCE

SIR,—I find the article (Aug. 29, p. 229) on Sir Russell Brain's book misleading when it turns " with Sir Russell towards the consideration of abstract or non-representational art in terms of the sense datum theory of perception ". Abstract art has three separate streams of origin, and the views you publish do not seem to apply to any of them.

The first group admittedly is not strictly non-representational but provides an " abstract " and usually unrecognisable rendering of an object all can see. Within this group it is interesting to recall that de Stael had no success at all with completely abstract painting but succeeded at once when he applied his method to the tangible world. A subdivision of this group choose an " abstract " object to treat in the same way, either a colour or a piece of geometry. Their intention is not really different, nor is the result. The second group comprises those paintings in which the artist has very obviously set out to cover an area of so many square inches or feet in as exciting a way as possible. There are many examples of these now operating, more or less exciting, or explosive. The third group are more interesting, and they have clearly seen what they set out to paint although it bears no resemblance to any recognisable object. They are distinguished from the previous group by the absence of obvious need to " cover " the area and by the presence of an " object ", of substance, with background, &c.

It is not certain whether it helps to bring in " physicochemistry ". But it is certain that of these three painters only the second can consciously set out to paint " emotion " or " feelings " alone, and it is understandable that his individual picture could describe his feeling at the moment of impact and his collected work his personality. The first man is a triple hybrid and his pictures must be a varying mixture of " impressionism by feature ", " expressionistic emphasis ", and " analysis ". What emotion is contained in the second of these elements is going to be clouded if not swamped by the other two.

The third group see an object and paint it. How come? Not very difficult really. Dante gave his tip in *Hell i* and admitted he looked at the midday sun. Bright light, with or without closed eyes, that gap between waking and sleeping, emotion perhaps, and now drugs, it is easy enough to find these objects. Presumably they have a cortico-physicochemical origin and bear some relation to teichopsia. They can also be coloured although I believe teichopsia is usually not. The limitation of this group is that the " observer " sees the same kind of object each time, and is therefore driven to find his own variations, and being an " objective " painter he now finds himself in the first group.

Seen this way there is really no point of application for your correspondent, who says that " these artists are seeking to represent their feelings aroused via the physicochemical relationships envisaged by the sense datum theory ". It is true that the first group respond to " physicochemistry " but positively diminish its " feelings " because they must indulge in " impressionism of feature " and " analysis " or they remain representational. When it comes to emotion in painting it is the " realists " who win every time: there is nothing colder than analysis.

The second group should strongly deny that they started with any " physicochemistry ", either for their past or their intended venture; they must imagine at the outset that their cortex is as clean as the canvas; presumably they generate " physicochemistry " from their labours as they go, but if they are honest they should not let it alter their intention. In this connection it can be said that one of their best performers is known to be nearly blind, which is quite permissible. The third group has a spontaneous charge of " physicochemistry ", which he paints, but " feelings " do not enter his performance more than that of any other " objective " painter, nor has he much right to claim that his " feelings " produce the object and therefore the " physicochemistry ", which in any case is the reverse of what your review describes. Altogether, the explanation in the article does not seem to satisfy these primary categories.

Manchester. OLIVER JELLY.

SIR,—When an article states that " no informed reasoning person can disagree ", and that something " must be regarded as incontrovertible ", then it is as well to suspect dogmatism and be prepared for a sleight-of-hand against logic. This occurs in the exposition of the sense datum theory in the review (Aug. 29, p. 229) of Sir Russell Brain's new book.

Physicochemical changes in the cerebral cortex may be a necessary condition for a perception to occur, but they are certainly not a sufficient condition as the sense datum theory implies—" perception being the end result of a series of physical events, the last of which is, in fact, a state of activity of the brain of the percipient ".

The theory collapses because it takes no account of the series of events which make the perceiver attend to a perception. Is the perceiver separate from his perceptions? Can the perceiver perceive himself perceiving? If he can, then, according to the sense datum theory, the perceiver must be a series of events in his own cortex, so how can these be separated from the series of events which lead up to the perceiving of the perception? If, on the other hand, it be said that the perceiver cannot perceive himself perceiving, then the perceiver is a concept and it is difficult to see how a concept can be acted on by physicochemical events.

The neurologist often cannot say whether a person is having perceptions or not, as, for example, in sleep; an individual may have perceptions throughout the night (i.e., dreams) but in the morning have completely forgotten them. An observer watching this individual sleeping would be unable to say whether he was dreaming; he could only ask afterwards whether he remembered his dreams.

Thus, neurology can give only a partial account of perception and any theory of perception based on neurology alone must be untrue.

London, N.21. J. M. HEATON.

## THE MALE ANENCEPHALIC FŒTUS

SIR,—I was interested in Dr. Polani's suggestion (Aug. 29) that an early miscarriage-rate of male anencephalics might explain the disturbed sex-ratio near term. The male anencephalic fœtus is interesting for a further reason, it may give information on the role of the fœtal pituitary gland in the development of the genital tract. Although Jones [1] has suggested tentatively that the abnormality of the brain and adrenal gland may both arise from a placental defect, the older idea that the abnormalities found (for example, the small adrenal and the enlarged thymus) are secondary to the lesion of the brain and pituitary gland still stands and is in line with the experimental evidence that removal or destruction of the fœtal pituitary gland in the rabbit, rat, and mouse results in a failure of normal adrenal development.[2] Further, in

1. Jones, I. C. The Adrenal Cortex. Cambridge, 1957.
2. Jost, A. *Cold Spring Harb. Symp. Quant. Biol.* 1954, **19**, 167.

similar experiments in the rabbit and the rat fœtus (to be published) I have found that the thymus gland is larger than in control fœtuses.

Jost [2] also showed in the rabbit that removal of the fœtal pituitary gland in the male at an early stage resulted in partial feminisation of the genital tract and is interpreted as due to the functional failure of the fœtal testis in the absence of the fœtal pituitary. Jackson and Hoffenberg [3] have described a case of congenital hypopituitarism with male pseudohermaphroditism in which they postulated that the abnormality of the genital tract was the result of intrauterine failure of the pituitary gland to produce gonadotrophin.

These observations make it reasonable to suppose that male anencephalics may show incomplete development of the genital tract. In my own series of nine male anencephalics, although five show reasonable development, in four there is marked hypoplasia of the external genitalia. This would seem to confirm the view that the functional activity of the fœtal testis is at any rate to some extent under the control of the fœtal pituitary gland in the human.

Department of Anatomy,
Middlesex Hospital Medical School,
London, W.1. J. G. BEARN.

## VARICOSE VEINS

SIR,—Your editorial of Sept. 19 painted a vivid picture of the surgeon's dilemma at this juncture thus: "Usually the surgeon, having dealt with the long (internal) saphenous vein, has two alternatives. He can either turn the patient on his face, rescrub, and retowel; or, with the aid of sandbags, spotlights, and elastic bandages, he can insinuate a scalpel and an artery-forceps or two where textbooks say the short saphenous joins the popliteal vein."

This problem is very pressing in a general surgical list. The first alternative is wearisome, the second unsatisfactory and the third, not mentioned (i.e., to do the lesser system some other day), is not usually available.

The labour of turning is, therefore, one of the main drawbacks to thorough surgery. To avoid the mental and spiritual inertia that greet the need to turn the patient after a lengthy operation on the long saphenous system, I carry out the lesser saphenous procedure first, which is usually less time-consuming, though extensive. I have, also, found the following drill expeditious and helpful. The principle was suggested by Mr. D. F. G. Bentley, theatre superintendent, and the details supervised by Dr. J. R. Elliott, consultant anæsthetist.

(1) The patient is brought into the theatre on a trolley.

(2) The operating table, covered by a non-slip mattress, is lowered below the level of the trolley.

(3) The patient is rolled over easily on to his face, down on to the lower level of the table, its head end being tilted down a few degrees and padded by a pillow.

(4) The necessary procedures on the lesser saphenous system are carried out.

(5) The incisions are sealed with 'Nobecutane'.

(6) The table is now raised above the level of the trolley which is wheeled in by suitably attired porters—the operating team standing back. A sterile towel is placed on the trolley at the level of the legs.

(7) The patient is rolled back to the lower level of the trolley, the legs coming to rest on the sterile towel.

(8) The patient is now lifted back to the table, using stretcher poles. The leg is now neatly and cleanly available for elevating, painting, towelling, and operating on the long saphenous system.

This drill sounds elaborate in description, but in practice works well and rapidly, and takes the uncertainty, unsterility, and difficulty out of turning even the heaviest patients.

New Cross Hospital, Wolverhampton. HENRY B. YOUNG.

SIR,—From your leading article there seems little doubt that elimination of incompetent perforating veins is a major step forward in treatment.

An effective non-operative method of doing this, in over 400 cases, has been subfascial perivenous injection of sclerosing solution (15% phenol in oil) at the sites of the perforators which can be easily determined clinically.[1] Effective blockage of the perforators leads, in six or eight weeks, to marked regression of the varicosities on the surface, together with relief of symptoms.

The Memorial Hospital,
Peterborough. D. W. BRACEY.

## THESAUROSIS FOLLOWING INHALATION OF HAIR SPRAY

SIR,—In reply to criticism by Mr. Greenfield, Dr. Morgan, and Dr. Leonard (Sept. 19) of my article of Aug. 15, may I say that I am aware that shellac (see discussion in my report) is still used in the manufacture of sprays, but I do not see why Mr. Greenfield makes a point of it; lac could hardly be more desirable than P.V.P. as a fixative. And may I add that, as a guard against bias, I wrote my report some considerable time before I knew the formulæ of the sprays used by my patient. These were subsequently imparted to me by their makers in confidence. One of them confirmed my suspicions.

Dr. Morgan's letter is inaccurate on several points. The time of exposure was not two weeks before she was seen but twelve months prior to her interview with me. She had been well before using the sprays, and cough and malaise had developed during their use. Both had gradually diminished after she discontinued them. Blood, urine, skin, and radiological examinations were done. The Mantoux test was mildly positive to O.T. 1 : 1000. The diagnosis of sarcoidosis was considered, but was discarded in view of the positive tuberculin reaction. Dr. Morgan may have been more fortunate than I, but I have yet to see a case of sarcoidosis with a positive Mantoux reaction. In this case there was nothing to indicate the presence of Boeck's disease and the patient's indisposition seemed clearly to be one of cause and effect.

I am obliged to Mr. Greenfield and Dr. Leonard for bringing to my notice the papers by Draize et al. and regret I was not aware of them at the time I wrote my report. It is satisfactory to know that no long-term hazards were found as a result of their experimental studies, but I submit that it would be an act of rashness to claim that in uncontrolled conditions the injudicious use of hair spray cannot lead to the deposition of particulate matter in the respiratory surfaces. We have no data of X-ray findings in the thousands of women who use fixatives every day, either in their homes or at the hands of their hairdressers.

My report is that of a clinical case met with in a busy and varied hospital practice in which it was found that vigorous use of hair fixatives was accompanied by the development of respiratory and constitutional symptoms. The coincidence of pre-spray health and post-spray malaise, with symptoms abating when spraying was abandoned, is too pointed to be ignored. In spite of adverse criticism from the sidelines something must be left to mature clinical judgment and I stand by the diagnosis made in this lady's case. If subsequent events prove me wrong I will make a public avowal of the fact. Meantime, I advise the sex to use hair sprays with caution and respect. I realise that by so doing I am sticking my neck out to the collective chopper of Mr. Greenfield, Dr.

3. Jackson, W. P. U., Hoffenberg, R. *Lancet*, 1956, ii, 1237.

1. Bracey, D. W. *Brit. med. J.* 1958, ii, 110.

Morgan, Dr. Leonard, and Draize and his coworkers on the merits or demerits of a single case. I am willing to risk decapitation.

Folkestone. B. G. EDELSTON.

## HÆMOPHILIA A IN A "GIRL" WITH MALE SEX-CHROMATIN PATTERN

SIR,—In your issue of Sept. 5 Professor Waldenström and his colleagues report the occurrence of hæmophilia A in a girl with a male sex-chromatin pattern. They mention that the homozygous hæmophiliac state in the female can result from the marriage of a hæmophiliac man to a woman who is a carrier of the disease. They cite a case described by Merskey [1] in 1951. In this family, which was reported first by Sir Frederick Treves [2] in 1886 and subsequently by Handley and Nussbrecher,[3] there are a number of anomalous features. In addition to the presence of a deficiency of antihæmophilic globulin, three of the patients have positive tourniquet tests and in one there is a prolonged bleeding-time.

The mode of inheritance in the first four generations of this family is most unlike that of a classical hæmophilia, there being direct transmission of the disorder from father to son. In the fourth generation there is a marriage of an affected male to his first cousin and the hæmorrhagic state is transmitted to their progeny in a similar autosomal dominant manner.

There would appear to be sufficient evidence to consider this family an example of "a capillary disorder associated with antihæmophilic globulin deficiency" [4–6] and not classical hæmophilia.

Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford. L. S. VALBERG.

## STRESS DISORDERS

SIR,—I feel sure that most clinicians will applaud Dr. O'Neill (Sept. 12) in his ventures into the difficult territory of stress. One is tempted to believe that we are on the verge of a revolution in medical science comparable with those brought about by Harvey and Pasteur. But certain points in Dr. O'Neill's lecture are unsatisfactory.

His definition of stress as the internal or resisting force brought into being in the human organism by interaction with the environment means everything and therefore nothing.

His definition of stress disorder in terms of its relationship with stress often applies to many diseases such as tuberculosis and cardiovascular disease which are not usually considered as belonging to this category.

A relationship must be established between stress and other fields of knowledge such as anatomy, physiology, and pathology. It is unacceptable to have two separate medical sciences, each with its own terminology, one reserved for the use of psychiatrists and the other for those who are concerned only with organic disease.

I venture to suggest that these defects in an otherwise admirable discourse could be rectified as follows:

Stress could be defined as nervous strain engendered in the course of adaptation to an environment for which mankind has been insufficiently equipped in the course of evolution. It is not suggested that modern life is particularly difficult: it is not the kind of life to which mankind has hitherto been accustomed. This definition takes into account the apparent correlation between so-called stress-disorders and the degree of "civilisation" to which the population has been subjected. Instead of seeking to distinguish two classes of disease, one of which is caused purely by stress and the other not, it is surely preferable to establish the role played by stress amongst all the multiplicity of other factors such as nutrition, infection, and trauma which may operate in any given case.

The so-called stress disorders should be considered in the usual way in terms of anatomy and physiology. When the principal disorders of this category, such as peptic ulceration, hypertension, asthma, neurosis, and depression, are considered as a group, one common feature is outstanding: derangement of conditioned reflex activity. When this is considered in relation to the pathology, symptomatology, and novel features in the environment it would seem possible to envisage in rough outline a theory of the pathology of stress which is compatible with the rest of medical science.

I believe that, subject to these necessary scientific disciplines, the keen observations of Dr. O'Neill and others of the same school will be of inestimable service to the human race in its difficult task of adjustment to twentieth-century life.

Sheffield. C. H. FOGGITT.

## DEATH AFTER ELECTROPLEXY

SIR,—The implication that suxethonium was the cause of death of the patient described by Dr. Campbell in your issue of Sept. 19 overlooks the most likely actual cause—poisoning by carbon dioxide.

No mention is made of how this patient was ventilated, but if 5% carbon dioxide was given presumably no soda-lime absorber was used during the five hours she survived. Immediately it is apparent that paralysis is prolonged for more than ten minutes such a patient should be intubated and given efficient ventilation by apparatus which includes a soda-lime absorber, and the temptation to inject any drug should be resisted.

To advocate an infusion containing over 50 mEq. of potassium—about four times the total plasma-potassium in an adult—to be given in $^1/_4$ hour is surely wrong. It would be more likely to make easier the search for reports of deaths than to be of any benefit to the patient.

Southampton. P. J. HORSEY.

## MONITORING THE HEART OF THE FŒTUS AND THE NEWBORN

SIR,—In his article of Sept. 5, Mr. MacRae has overlooked some important aspects of the story.

In the interests of historical accuracy it should be known that the first instance of the relaying of the fœtal heart-sounds on a loudspeaker was recorded by Falls and Rockwood.[1]

This work was followed by many others, of which, in my opinion, the most important papers were Frederick and Dodge,[2] Cioslowski [3], Smith and Hervert,[4] and finally, in 1953, Gunn and Wood,[5] quoted by Mr. MacRae.

All these workers had trouble with extraneous noise and acoustical feedback and used large and costly instrumentation. In 1955, therefore, I concentrated on the design of a small microphone which would substantially receive sounds only from objects with which it was in contact and would be sensitive down to very low frequencies. The next step was the design of a small high-gain amplifier incorporating continuously variable high and low frequency attenuators.[6,7]

During a series of experiments conducted by Dr. A. B. Kinnier Wilson in 1957, he demonstrated in my presence the fœtal heart-sounds of a patient of Robert Nevill's at full loudspeaker strength with a clarity of tone which I have yet to hear surpassed. Simultaneous phonocardiographic recordings of the

1. Merskey, C. *Quart. J. Med.* 1951, **20**, 299.
2. Treves, Frederick. *Lancet*, 1886, ii, 533.
3. Handley, R. S., Nussbrecher, A. M. *Quart. J. Med.* 1935, **4**, 165.
4. Alexander, B., Goldstein, R. *J. clin. Invest.* 1953, **32**, 551.
5. Larrieu, M. J., Soulier, J. P. *Rev. Hémat.* 1953, **8**, 361.
6. Valberg, L. S., Brown, G. M. *Medicine*, 1958, **37**, 181.

1. Falls, F. H., Rockwood, A. C. *J. Amer. med. Ass.* 1923, **81**, 1683.
2. Frederick, H. A., Dodge, H. F. *Bell Syst. techn. J.* 1924, **3**, 531.
3. Cioslowski, T. *Ginek. Polska* **11**, 684.
4. Smith, A. L., Hervert, A. B. *Amer. J. Obstet. Gynec.* 1940, **40**, 162.
5. Gunn, A. L., Wood, M. C. *Proc. R. Soc. Med.* 1953, **46**, 85.
6. Taylor, S., Fothergill, L. *Lancet*, 1956, i, 1050.
7. Kinnier Wilson, A. B., Fothergill, L., Taylor, S. *ibid.*, 1956, ii, 1027.

foetal and maternal hearts were made at the same time, confirming the purity of the acoustical response. Having reached this point, I was satisfied that the clinical use of this method depended thereafter on the application of known principles.

I should like to acknowledge the assistance of Mr. S. H. Parsonage in obtaining the recordings mentioned above, and Mr. Thomas Thirsk of Croydon, now retired, who carefully manufactured the 'Soniscopes' and microphones used by Dr. Kinnier Wilson and Mr. MacRae, and of many others who have helped in this development. Like all similar applications, success is almost always the result of good teamwork.

Selsey, Sussex. LIONEL FOTHERGILL.

## HOW MANY MOUTHS?

SIR,—Your leader of Sept. 19 has suggested to me a daring speculation. We have now reached the stage when an oral inhibitor of conception, by action either on ovary or testis, is a practical possibility—in other words, birth prevention by hormone control. Should we not now aim at a further step, the discovery of a hormone modifier that would abolish libido? Theoretically it should be something that could be added to bread like calcium, to water like fluoride; and those who for a sufficiently good reason were permitted by authority to incur the possibility of conception would be allowed for the time being a ration free from the anaphrodisiac ingredient. This would make the late George Orwell's dream of an anti-sex league an effective reality, and while a few might think the invention more appropriate for other people than for themselves, it would be a splendid refutation of any charge of hedonism if birth-control enthusiasts were to concentrate their energies upon research along lines such as these.

I have an intuition that the moral theologians would look as much askance at this idea as at other means of artificial birth prevention, since the essence of virtue, sexual and every other, is not to be without desire but effectively to discipline it. I am, however, concerned in this context solely with science.

Health Department, Darlington. JOSEPH V. WALKER
Medical Officer of Health.

## IMIPRAMINE

SIR,—I should like to endorse Dr. Strauss's remarks (Sept. 19) on the value of uncontrolled pilot studies, for in these one acquires the "feel" of a drug and perhaps some finesse in handling it. However, the public acceptability of a personal clinical conviction varies with the distinction of the author, so that most of us must have recourse to chi-squared.

Nonetheless, as the drug treatment of depressive states is being discussed at the moment, there is a further conclusion we should like to add. This is that imipramine ('Tofranil') is much more likely to prove successful in a retarded than in an agitated depression. In the latter state the agitation is often increased intolerably: this may be controlled, as Dr. Zelmanowits (Sept. 19) stated, by chlorpromazine; or it may not. A drug therapy more likely speedily to ameliorate and even abolish the symptoms of agitated depression is the combination of amylobarbitone and bemegride ('Mylomide 100') without manifest hypnotic effect. The pharmacology of this is by no means clear.

In answer to Dr. Zelmanowits's doubt of our assertion that imipramine acts centrally, we take the view that sleep and psychomotor activity are central functions, that a drug reducing the former and increasing the latter does so by central stimulation, and that the generalised jactitation seen in overdosage indicates excitation in the cord and brain-stem—see Dr. Gittleson's case (Sept. 19).

Dr. Zelmanowits hypothesises that imipramine and phenothiazines have a causal therapeutic effect on the physiology behind the psychopathology of depressive and schizophrenic disorders.

We take the view, which we feel is implicit in Dr. Strauss's letter, that these drugs (*a*) abolish symptoms until a natural remission occurs, and (*b*) by reduction of anxiety may facilitate and expedite a remission.

Herrison Hospital, Dorchester, Dorset. R. H. BOARDMAN
A. G. FULLERTON.

## BIOCHEMICAL EFFECT OF PHENYLACETIC ACID

SIR,—The papers by Dr. Sandler and his colleagues (Sept. 12) are of great scientific interest, but they do not prove that phenylacetic acid inhibits 5-hydroxytryptophan decarboxylase in vivo.

The investigations started with the demonstration by Davison and Sandler [1] that phenylacetic acid partially inhibited 5-hydroxytryptophan decarboxylase in homogenates of guinea-pig kidney in vitro. The lowest concentration of the inhibitor used was 50 μmol. per 3 ml., and this caused a 68% inhibition of the action of the enzyme. This concentration equals 2·25 g. phenylacetic acid per litre. The dosage of phenylacetic acid given to adult patients with the carcinoid syndrome was 5 g. by mouth. If the acid is distributed through the whole body water, this corresponds to a maximum concentration of the acid in body fluids of about 125 mg. per litre. In actual fact the true concentration will always be lower than this because phenylacetic acid is very rapidly conjugated to phenylacetylglutamine, which is quickly excreted in the urine. The rate of conjugation is so rapid that it is usually impossible to detect any free phenylacetic acid in blood or urine. Ambrose et al.[2] reported a 100% recovery of the conjugates of ingested phenylacetic acid in urine, 95% being phenylacetylglutamine and 5% glucuronide. There is no evidence that phenylacetylglutamine inhibits 5-hydroxytryptophan decarboxylase either in vitro or in vivo, although this would physiologically be more relevant than inhibition by free phenylacetic acid. Therefore, the only relevance of the in-vitro experiments of Davison and Sandler to the therapeutic trial of phenylacetic acid in the carcinoid syndrome was the suggestion that this substance should be used.

The biochemical results obtained in the patients indicate that there was a temporary reduction of the urinary output of 5-hydroxyindolylacetic acid (5-H.I.A.A.) in four out of six cases, and a reduction of 5-hydroxytryptamine (5-H.T.) in one case after ingestion of phenylacetic acid. This is assumed to indicate reduced production of these compounds by decarboxylation of 5-hydroxytryptophan, whilst the possibility of a temporary reduction of their clearance in the urine is never considered. More accurate information is available of the mechanisms of excretion of 5-H.I.A.A. than of 5-H.T., and therefore only the former substance will be discussed. 5-H.I.A.A. is excreted by proximal tubular secretion [3] similar to diodrast, penicillin, and many conjugates of organic acids. The clearance of all these substances is specifically reduced by probenecid. In addition, they show the phenomenon of mutual competitive inhibition of the tubular transport system, excretion of large quantities of any one substance being associated with reduced clearance of the others. It is not known whether phenylacetylglutamine is such a competitive inhibitor, but this is likely from comparison with closely allied compounds. Thus, benzoylglycine (hippuric acid) and *p*-aminophenylacetylglycine are excreted by proximal tubular secretion,[4] and would undoubtedly compete with 5-H.I.A.A. for excretion.

1. Davison, A. N., Sandler, M. *Nature, Lond.*, 1958, **181**, 186.
2. Ambrose, A. M., Power, F. W., Sherwin, C. P. *J. biol. Chem.*, 1933, **101**, 669.
3. Despopoulos, A., and Weissbach, H. *Amer. J. Physiol.*, 1957, **189**, 548.
4. Smith, H. W., Finkelstein, N., Aliminosa, N., Crawford, B., Graber, M. *J. clin. Invest.* 1945, **24**, 388.

Knoefel and Huang [5] have recently reported a detailed study of the structure-activity relationship of substances involved in proximal tubular transport. The aminoacid involved in the conjugation was shown to be relatively unimportant. Thus, benzoyl L-α-alanine, benzoyl D-α-alanine, benzoyl DL-β-aminovaleric acid, benzoyl DL-α-aminophenyl-acetic acid, and benzoyl α-alanine resembled benzoylglycine in proximal tubular secretion, selective accumulation in renal cortex, and inhibition of *p*-aminohippurate transport. It is therefore extremely likely that phenylacetylglutamine is a compound of the same type.

The doubt could have been settled if other comparatively simple biochemical investigations had been included.

For example, if the effect is due to enzyme inhibition, the concentration of 5-H.I.A.A. in plasma would be expected to fall in parallel with urinary 5-H.I.A.A.; if due to reduced urinary clearance plasma 5-H.I.A.A. would rise. Determination of 5-H.I.A.A. in plasma is impossible by current techniques in normal subjects, but can be carried out in patients with carcinoid syndrome [6] where the concentration of the acid is greatly increased above normal values. Alternatively, an infusion of *p*-aminohippurate (P.A.H.) could easily have been included in the experimental design. If the ingestion of phenylacetic acid reduces proximal tubular secretion of 5-H.I.A.A., the P.A.H. clearance would fall in step with the reduced output of 5-H.I.A.A. If the effect is due to enzyme inhibition, as postulated by the authors, the P.A.H. clearance would remain unchanged. In some of the patients, although excretion of 5-H.I.A.A. was temporarily reduced after a single dose of phenylacetic acid, the output of 5-H.I.A.A. returned to control values on continuous therapy. This is strongly in favour of an effect on the renal clearance of 5-H.I.A.A. Increased blood levels of the acid would maintain the urinary output of the acid at control values despite a lowered clearance.

A similar observation caused confusion about ten years ago. Wolfson et al.[7] reported reduction of urinary 17-ketosteroid output in patients suffering from gout, and considered that this might be of importance in the physiological disorder of the disease. Two years later, Gardner et al.[8] showed that 17-ketosteroid output is reduced to 50% of control values by treatment with probenecid, again presumably by inhibition of proximal tubular secretion. Probenecid similarly reduces the output of 5-H.I.A.A. both in normal subjects and in patients with the carcinoid syndrome.[3]

It is hoped that future more precise observations will soon resolve the doubt whether the effect of phenylacetic acid in the carcinoid syndrome is of fundamental importance in enzyme biochemistry, or whether it is of as little consequence as the reduction of 17-ketosteroid output in treated cases of gout.

London, W.12. M. D. MILNE.

5. Knoefel, P. K., Huang, K. C. *J. Pharmacol.* 1959, **126**, 296.
6. Sjoerdsma, A., Weissbach, H., Terry, L. L., Udenfriend, S. *Amer. J. Med.* 1957, **23**, 5.
7. Wolfson, W. Q., Guterman, H. S., Levine, R., Cohn, C., Hunt, H. D., Rosenberg, E. F. *J. clin. Endocrinol.* 1949, **9**, 497.
8. Gardner, L. I., Grigler, J. F., Migeon, C. J. *Proc. Soc. exp. Biol., N.Y.* 1951, **78**, 460.

# Obituary

## DENNIS HERBERT GEFFEN

O.B.E., M.D. Lond., D.P.H.

Dr. Geffen, medical officer of health for St. Pancras, who died on Sept. 17, belonged to the generation of medical officers of health who carried through the expansion of the personal health services in public health in the period immediately after the first world war, following the earlier generation of sanitarians.

He was born in London and educated at University College School and University College Hospital. After qualifying in 1919 he held house-appointments at U.C.H., St. Marylebone Hospital, and Chelsea Hospital for Women. In 1921 he took the D.P.H. and the following year he started his career in public health on the staff of the London County Council. In 1922 he became assistant tuberculosis officer for Poplar, and later he became assistant M.O.H. for Finsbury. Before he took up his appointment at St. Pancras he was for some years M.O.H. for Enfield.

His public-health and medical interests were wide. He was a postgraduate and undergraduate lecturer on public health at the Institute for Child Health and at University College Hospital respectively. He was a member of the board of governors of the Royal Free Hospital, and at the time of his death was about to begin his second year of office as chairman of the Metropolitan Boroughs Medical Officers' Committee. He was a vice-chairman of the National Baby Welfare Council and an honorary medical officer of the Save the Children Fund.

V. F. writes:

"As M.O.H. to the rapidly growing district of Enfield in the 'twenties and 'thirties, Geffen applied himself with enthusiasm to the development of the maternal and child welfare services in particular, and he was closely associated with the foundation of the National Baby Week Council. When he came to St. Pancras, he succeeded another maternity and child pioneer, the late Maitland Radford. It is a coincidence and a sad fact that neither of them was granted the fortune of completing his full years of office, let alone enjoying a period to follow of rest and retirement. Although maternal and child health was perhaps Geffen's major interest in his earlier M.O.H. years, he threw himself with enthusiasm and abundant energy into all aspects of the public-health field as the problems arose. This was just as well from his own point of view, since the separation of the personal health services from the environmental, by their transfer from the borough to the county authority in London after July, 1948, was for him in particular a deprivation and frustration of his past public-health life and work not easy to bear with equanimity.

"Whatever he tackled, he did with enthusiasm and thoroughness. He was one of the first in this country to point out the association between provocation poliomyelitis and recent diphtheria/pertussis inoculation which occurred in a number of cases in London in 1949. He took a particular interest in poliomyelitis, and wrote and spoke on this fascinating infection both in this country and at international congresses abroad. In fact, when he became ill in August, he was about to leave to deliver a paper in Munich on poliomyelitis in early infancy.

"Geffen fully appreciated also the importance of the environmental services. Despite the statutory limitations of Metropolitan boroughs, he developed a borough geriatric service, together with his deputy, Dr. Tracy, which was comprehensive in many respects, and he spent much time personally and made far-reaching recommendations in connection with local problems of housing, atmospheric pollution, and health education. Because he was a first-class committee man, prepared to give a clear, incisive, and well-reasoned opinion, as befitted one who was also a barrister, he was in much demand, and spent much time ungrudgingly on many committees, medical and medicosocial, official and voluntary.

"Geffen, as might also be expected, was a fluent speaker and in considerable demand for social occasions. He also wrote many papers, and even found time to write several textbooks, either alone or in collaboration. He enjoyed a round of golf when he could, and a knowledgeable and discriminating appreciation of pictures and antiques was a hobby which he also enjoyed exercising."

Dr. Geffen leaves a widow and two sons.

# Notes and News

## MEDICAL RESEARCH COUNCIL OF IRELAND

STRETCHING of the "elastic shoestring"[1] is evidently not confined to research in Great Britain; for the report of the Medical Research Council of Ireland,[2] besides recording progress in established research, contains exciting plans for new surveys of perinatal mortality and cancer chemotherapy—all on a total annual budget of £31,707. In point of fact, however, the Council faces a contraction of its activities unless a larger grant is forthcoming. The Minister of Health has been able to raise the annual grant by only £4000 and the total grant will now be fixed for the next five years. But, as the report points out, the cost of living is bound to go on rising, and it seems inevitable that the number of grants will have to be reduced. If the average stipend becomes any lower it will be impossible to recruit new members, and already many young workers are taking research posts abroad through lack of opportunity in Ireland.

Among much of interest in the present report may be mentioned the work on trace metals and tuberculosis.

Mr. Winder and Mrs. Pigott have found that, grown on a medium moderately deficient in iron or zinc, *Mycobacterium smegmatis* became longer, with a lower ratio of nucleus to cytoplasm. Moreover, the cellular concentration of deoxyribonucleic acid (D.N.A.) was only 25% of normal, although that of ribonucleic acid was normal. Further research is in progress to see if these trace metals are required directly for D.N.A. synthesis, or whether they control nuclear division indirectly.

Some think that the antibacterial action of isoniazid is mediated by its oxidative breakdown inside the tubercle bacillus, and the effect of the free radicals thereby produced on intracellular enzymes—particularly catalase and peroxidase. The Dublin workers have found that copper is the most active metal ion catalysing the action of isoniazid on catalase; possibly, therefore, inactivation takes place in the same way.

Prof. Oliver FitzGerald reports continuing studies on serum-amylase and serum-lipase in toxæmia of pregnancy. In normal subjects the blood level of both enzymes rises at the end of pregnancy, but this does not happen in women with toxæmia. The Dublin workers suggest that the incidence of pancreatitis may be lower in toxæmic patients, and are to investigate these results further with particular reference to serum lipids and lipoproteins in pregnancy.

## APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

| *Approved name* | *Other names* |
|---|---|
| Ambutonium Bromide | (3-Carbamoyl-3:3-diphenylpropyl)ethyl-dimethylammonium bromide |
| Chlorthenoxazin | 2-2′-Chloroethyl-2:3-dihydro-4-oxobenz-1:3-oxazine |
| Diamthazole | 6-2′-Diethylaminoethoxy-2-dimethylamino-benzothiazole<br>Asterol is the dihydrochloride |
| Diethyltoluamide | *NN*-Diethyl-*m*-toluamide |
| Dodicin | 2:5:8-Triazaeicosane-1-carboxylic acid<br>Dodecyl-di(aminoethyl)glycine |
| Ethionamide | 2-Ethyl*iso*nicotinthioamide |
| Flumethiazide | 7-Sulphamoyl-6-trifluoromethylbenzo-1:2:4-thiadiazine 1:1-dioxide |
| Guaiphenesin | 3-*o*-Methoxyphenoxypropane-1:2-diol<br>Guaiacol glycerol ether<br>Respenyl |
| Haloperidol | 4-*p*-Chlorophenyl-1-(3-*p*-fluorobenzoyl-propyl)-piperidin-4-ol |
| Kanamycin | An antibiotic produced by *Streptomyces kanamyceticus*<br>Kantrex |
| Metahexamide | 1-(3-Amino-4-methylbenzenesulphonyl)-3-*cyclo*hexylurea<br>Euglycin; Melanex |
| Metformin | *N′N′*-Dimethyldiguanide |
| Methaqualone | 2-Methyl-3-*o*-tolyl-4-quinazolone<br>Melsedin is the hydrochloride |
| Methazolamide | 5-Acetylimino-4-methyl-2-sulphamoyl-1:3:4-thiadiazoline<br>Neptazane |
| Phenformin | *N*[1]-Phenethyldiguanide<br>D.B.I. |
| Propyl Docetrizoate | Propyl 3-diacetylamino-2:4:6-tri-iodobenzoate |
| Proxyphylline | 7-2′-Hydroxypropyltheophylline<br>Brontyl |
| Sulphasomizole | 5-*p*-Aminobenzenesulphonamido-3-methyl*iso*thiazole |
| Thioridazine | 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-methylthio-phenothiazine<br>Melleril is the hydrochloride |

1. *Lancet*, 1959, ii, 77.
2. Medical Research Council of Ireland. Annual Report for 1958. From 50, Merrion Square, Dublin.

INDEX

| *Proprietary name* | *Approved name* | *Proprietary name* | *Approved name* |
|---|---|---|---|
| Asterol | Diamthazole | Melanex | Metahexamide |
| Brontyl | Proxyphylline | Melleril | Thioridazine |
| D.B.I. | Phenformin | Melsedin | Methaqualone |
| Euglycin | Metahexamide | Neptazane | Methazolamide |
| Kantrex | Kanamycin | Respenyl | Guaiphenesin |

## THE UNESTABLISHED

IN medicine—as perhaps in most other callings—those who have not yet gained a secure and satisfactory professional position sometimes have difficulty in gaining a fair hearing. To remedy this defect the General Practice Reform Association (at first known as the Unestablished Practitioners' Group) was brought into being. The Association has lately published a leaflet [1] enumerating proposed changes.

The Association recommends that the maximum number of patients that a general practitioner may have on his list under the N.H.S. should be reduced by stages from 3500 to 2000 (and probably less in areas that are sparsely populated or have high morbidity) with compensatory adjustments in the capitation fee at each stage. The loaded capitation fee, says the Association, should be moved to cover the first 1000 patients on the list; and a basic expense allowance should be paid to all N.H.S. principals. Junior partners should be guaranteed on entry a share amounting to at least half that of the largest share in the practice, rising to parity in not more than five years; and the extra list of patients permitted for an assistant should be abolished, except in practices where a defined period of up to, say, two years is needed to enable the practice to grow and thus provide enough income for an additional partner. In new practices an initial practice allowance should be payable automatically wherever permission to start a new practice is granted: "A doctor should not be expected to conduct an experiment at his own expense on behalf of the N.H.S." In health centres doctors should be remunerated by salary or on a sessional basis.

Turning to hospitals, the Association says that staffing should be based on career posts. It suggests that all present senior registrars who have completed four years in this grade, all S.H.M.O.s, and most consultants should be placed in the single grade of hospital specialist, though with various degrees of seniority. The more senior consultants could be promoted to senior hospital specialist, and those of exceptional standing placed in the special grade of consultant. J.H.M.O.s, registrars, and senior registrars who have not completed four years in this grade should be merged into a single career grade of hospital medical officer. These doctors would have security of tenure in the hospital service, with increments of remuneration for length of service; promotion to hospital specialist would depend on seniority, ability, and qualifications.

1. Published by the executive committee of the Association, 39, The Avenue, London, N.W.6.

## Genetics, Statistics, and Radio-isotopes

The Institute of Basic Medical Sciences will hold a course on this subject from Oct. 19 to 21, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2. Further particulars may be had from the secretary of the institute, Mr. W. F. Davis, at the college.

### Royal College of Physicians of London

On Monday, Oct. 19, at 3 P.M., Sir Russell Brain will give the Harveian oration. The title of his oration is William Harvey, Neurologist. On Tuesday, Nov. 17, at 5 P.M., Sir Kenneth Clark will give the Lloyd-Roberts lecture. He will speak on Art and Society. Both lectures will be given at the college, Pall Mall East, S.W.1.

### Psychiatry for the General Practitioner

The National Association for Mental Health is holding a residential course for general practitioners on this subject from Nov. 13 to 15, at the Kenilworth Hotel, London, W.C.1. The speakers will be Dr. Desmond Curran, Dr. H. V. Dicks, Dr. J. J. Fleminger, Dr. T. F. Main, Dr. Felix Post, Dr. T. P. Rees, Dr. W. Linford Rees, Dr. H. J. Shorvon, and Dr. C. A. H. Watts. Further particulars may be had from the education secretary of the association, 39, Queen Anne Street, W.1.

### Mental Health—Today and Tomorrow

The Royal College of Nursing will hold a conference on this subject from Oct. 28 to 30, at Friends House, Euston Road, London, N.W.1. The speakers will be Mr. Derek Walker-Smith, the Minister of Health, Dr. R. F. Tredgold, Dr. J. P. Horder, Dr. Alfred Elliott, Dr. R. K. Freudenberg, Dr. Donald Macmillan, Dr. David Stafford-Clark, Dr. J. T. Keddie, Dr. Joshua Carse, and Dr. Peter Sainsbury. Application forms may be had from the conference secretary, Royal College of Nursing, 1a, Henrietta Place, W.1.

### International Federation of Surgical Colleges

A meeting of the Federation was held in Munich on Sept. 15 and 16, under the chairmanship of Sir Harry Platt. Working parties were set up on surgical missions, training of surgeons, surgical research, and the interchange of young surgeons.

The following new members were elected: College of Surgeons of Poland, Association of Surgeons of India, Association Française de Chirurgie, Société Hellenique de Chirurgie, Austrian Surgical Society, Swiss Surgical Association. The representative of the Polish College of Surgeons was elected to fill a vacancy on the executive committee. It was agreed to hold the next meeting in London in October, 1960.

### Anglo-German Medical Society

This society was set up at a meeting in London on Sept. 9 attended by German and British doctors. It was agreed that both countries would benefit by an exchange of doctors in every branch of medical science and practice, including general practice, and the chief aim of the society will be to collect funds for this purpose. The society also hopes to provide a medical information service through a quarterly newsletter. The following were elected members of the executive committee:

*British section.*—President, Prof. J. S. Mitchell (Cambridge); vice-president, Prof. W. Arthur Mackey (Glasgow); secretaries, Dr. E. Kawerau (London) and Dr. W. Walker (Dundee); treasurer, Dr. D. P. Winstanley (London).

*German section.*—President, Prof. H. Bennhold (Tübingen); vice-president, Prof. W. Lehmann (Kiel); secretary, Dr. F. K. Beller (Tübingen); treasurer, Dr. R. Grosz (Marburg).

### Prizes for Scottish Registrars

In 1958 the Western Regional Hospital Board agreed to provide annually, from its endowment resources, five prizes of £50 each which would be open to competition by the registrars in the regional hospitals. The first awards have been made to Dr. Shedden Alexander, Dr. T. S. R. Train, Dr. J. S. S. Stewart, Dr. A. I. M. Glen, and Dr. Eric Coleman.

### Prize for Medical Film

The *Presse Médicale* is again offering in 1960 a prize (frs. 100,000) for a medical 16 mm. film. Next year the prize will also be open to films subsidised or produced by a laboratory or firm. Entries should reach the secretariat of the journal, 120, boulevard Saint-Germain, Paris, VI, by Feb. 29.

### Medical Photography

On Thursday, Nov. 12, at 6.30 P.M., Dr. Hugh Clegg will open the exhibition which the medical group of the Royal Photographic Society is holding at 16, Princes Gate, London, S.W.7, from Nov. 12 to 19.

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On Friday, Oct. 2, at 3.30 P.M., at the Institute of Laryngology and Otology, 330, Gray's Inn Road, London, W.C.1, Mr. Anthony Radcliffe will give a lecture on tonsillectomy and adenoidectomy.

On Tuesday, Oct. 13, at 3 P.M., at the University of Leeds, Mr. Norman Fisher will give the inaugural lecture to the faculty of medicine. His subject will be culture and allergy.

The Association of Clinical Pathologists will hold a meeting from Oct. 1 to 3, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2. On Friday, Oct. 2, at 4.30 P.M., Prof. J. N. Cuming will give his presidential address on neurochemistry and neurochemists, and on Saturday, Oct. 3, there will be a joint meeting with the Association of Clinical Biochemists.

On Sunday, Oct. 4, at 10.15 A.M. at University College Hospital, London, W.C.1, there will be a meeting for general practitioners. Mr. T. D. Whittet will speak on a survey of new drugs and preparations.

The Middlesex Hospital Medical School will hold a refresher course from Oct. 2 to Oct. 4, and the annual dinner for past and present students will be held on Friday, Oct. 2, at 7.30 P.M., at the Savoy Hotel, London, W.C.2. Further particulars may be had from the medical school secretary.

The London Jewish Hospital Medical Society will meet on Thursday, Oct. 8, at 8.30 P.M., at 11, Chandos Street, W.1. Prof. John Yudkin will give the presidential address and his subject will be Rations and Irrationality.

The Professional Nurses and Midwives Conference and the London Nursing Exhibition will be held, under the auspices of the *Nursing Mirror*, from Oct. 12 to 16 at the Seymour Hall, Seymour Place, London, W.1.

The medical group of the Royal Photographic Society of Great Britain has collected 2000 classified abstracts of papers on photography in medicine and biology. The hon. librarian, Mr. J. A. Fairfax-Fozzard, F.R.P.S. (School of Anatomy, The University, Cambridge), will supply references, free of charge, to all bona-fide inquirers.

## Appointments

EDMISTON, D. R., M.B. St. And., D.P.H.: assistant M.O.H. and assistant school M.O., Oldham.
FISHER, G. W. H., M.B. Durh.: assistant M.O.H. and school M.O., Warwickshire.
HALSTEAD, A. H., M.B. Lond.: assistant M.O.H. and school M.O., Warwickshire.
MACGREGOR, CATHERINE S., L.R.C.P.E., D.P.H.: assistant M.O. (maternity and child welare), Glasgow.
ROY, J. R., M.B. Glasg., M.R.C.P.E., D.P.M.: consultant psychiatrist, St. Nicholas Hospital, Gosforth, Newcastle upon Tyne.
WATKINS, MELVILLE, M.R.C.S., D.P.H.: M.O.H., divisional school M.O., and area M.O., Walthamstow.
WOOD, MARGARET T., M.B. Birm., D.OBST., D.P.H.: assistant M.O. (maternity and child welfare), Wolverhampton.

**East Anglian Regional Hospital Board:**

KEOHANE, J. T. F., M.B. N.U.I.: E.N.T. registrar, Norfolk and Norwich Hospital and Jenny Lind Children's Hospital, Norwich.
ORCHARD, B. W., M.B. Lond., D.P.M.: assistant psychiatrist, Hellesdon Hospital.
PIMM, L. H., M.B. Lond., F.R.C.S.: consultant orthopædic surgeon, Ipswich and East Suffolk hospital group.
TERRY, M. F., M.B. Lond.: registrar in obstetrics and gynæcology, Ipswich and East Suffolk hospital group.

**Newcastle Regional Hospital Board:**

BURKITT, E. A., M.R.C.S., D.P.M.: consultant psychiatrist and deputy medical superintendent, Winterton Hospital, Sedgefield.
CRUMPTON, N. E., M.B. Durh., D.P.M.: assistant psychiatrist (S.H.M.O.), St. George's Hospital, Morpeth.
GOODWIN, M. A., M.B. Leeds, F.R.C.S.E.: consultant orthopædic surgeon, Darlington and Northallerton groups of hospitals.
PRATT, T. L. C., M.R.C.S., D.M.R.D.: consultant radiologist, Darlington, Northallerton, and North and South Tees-side groups of hospitals.

## Births, Marriages, and Deaths

### DEATHS

McPHERSON.—On Sept. 17, at Bradford Royal Infirmary, Barbara McPherson (Simonds), M.B., aged 40 years, of Fourways House, Hoddesdon, Herts.